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The Effect of Naltrexone on Memory Deficit Followed by Electroconvulsive Therapy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Electroconvulsive therapy (ECT) is famously known as a treatment for depression; however, memory impairments have always been a point of concern. The use of opioid antagonists may protect against the development of memory deficits after ECT. The current study aimed at assessing the effect of Naltrexone in diminishing memory impairments.
Methods: This randomized, double-blinded, placebo-controlled clinical trial took place at Imam Hossein hospital of Tehran/Iran. Patients diagnosed with MDD, were assigned to either Naltrexone or placebo and received 6 sessions of ECT within 2 weeks. Wechsler Memory Scale was performed the day before the first session of ECT, as well as 2 weeks, 1 and 3 months after finishing the 6th session. The Hamilton depression rating scale was performed 2 times to examine the possible interference caused by depression or to relapse as a confounding variable.
Results: Patients receiving Naltrexone and placebo showed no significant difference in WMS scores. However, after further assessment, changes of WMS scores in every round were compared; the results showed that after 2 weeks from baseline, the amount of the reduction of total WMS scores from baseline was significantly lower in the Naltrexone group (P = 0.04).
Conclusions: This study suggests that Naltrexone as compared to placebo has no advantageous effect on attenuating memory deficits in the long term. It is a smaller degree of memory decline that makes Naltrexone superior to placebo.

Keywords: Electroconvulsive Therapy, Memory Deficit, Naltrexone

1. Background

Electroconvulsive therapy (ECT) has been previously implicated as an effective method for treatment of serious psychiatric disorders, such as major depressive disorder (MDD) (1). Although the predominant evidence suggests that no brain damage is caused by ECT, some findings oppose the statement (2). Due to its adverse effects on memory and cognition, the high efficacy of this method has not been enough for physicians (3-5). The reported side effects, mainly include causalities in long-term memory and autobiographic, and also to a lesser degree in short-term memory (6). Some studies have reported that at least one-third of patients that receive ECT experience temporary or permanent memory dysregulation (7). Various mechanisms have been proposed as the cause of memory deficit after ECT. These include glutaminergic, alpha aminobutyric acid and gabaergic systems as well as cyclo-oxygenase, nitric oxide, and cholinergic pathways (8).

Many researchers have concluded that keen administration of opioids impairs learning and memory of behavioral tasks (9-11). Morphine-induced impairment may be the result of the effect of mu-opioid receptors, because the action of opioids might be inhibited by mu-opioid receptor antagonists (12). Lately, studies working on the impact of administration of opioid antagonists, such as naloxone and naltrexone, on memory expansion in lab animals have been performed (13, 14).

Naltrexone is an opioid antagonist that is related to all 3 opiate receptor sites (μ, κ, δ), as a function of dose administered. The plasma half-life of naltrexone is considered to be 10.5 hours; associated 6β-naltrexol has been reported to have a plasma half-life of 14 to 19 hours (15). The lucrative effect of naltrexone on spatial learning and

memory seems to be the result of augmenting GluA1-S845 phosphorylation-dependent AMPAR trafficking (16). Naltrexone and other toll like receptor 4 (TLR4) antagonists could cause an exquisite therapeutic method to reduce the main problems of memory or executive cognitive function disorder after cardiac arrest/cardiopulmonary resuscitation (14). In one of the few studies on humans, naloxone infusion compared with placebo had a positive impact on cognitive impairments of ECT (17). The evidences provide a foundation for the hypothesis that by manipulation of opioid systems, memory dysfunction after ECT could be reduced in affected patients.

2. Objectives

After paying attention to proposed mechanisms and approved positive effects on lab animals; the researchers of the current study assessed the impact of oral agent "Naltrexone" on reducing memory deficit after electroconvulsive therapy in comparison with placebo in human subjects.

3. Methods

This clinical randomized, double-blinded, and placebo-controlled trial was accomplished in Imam Hossein hospital of Tehran/Iran, from June 2015 to March 2016. The population of this research included all adult MDD patients, candidates for ECT, who were aged 18 to 66 years old and were admitted to the psychiatry ward of Imam Hossein Hospital (Shahid Beheshti University of Medical Sciences). The patients under study were diagnosed with major depression disorder (MDD) by a psychiatrist based on structured clinical interview for DSM disorders (SCID-I) (18) in both in/out-patient conditions.

The inclusion criteria were having MDD or BMD based on diagnostic and statistical manual (DSM)-5 criteria, age of 18 to 65 years, and recommendation of ECT by a psychiatrist. Patients were excluded from the study if they were affected by a prominent medical condition, diagnosed with schizophrenia or bipolar mood disorder, or had a history of ECT in the last 6 months. Additional exclusion criteria included history of seizures, neurocognitive disorders, and drug or alcohol misuse in the previous 12 months.

Through the structured interview, a number of patients were diagnosed with MD. Among them, patients, who volunteered to attend the research and met the inclusion criteria were chosen and invited to participate in the study. After participating in the information session and providing written informed consent forms, the participants were registered and attended ECT sessions.

There was an attempt among the 2 groups to reject the null hypothesis of no difference in memory deficit followed by ECT, at type I error level (α) of 0.05 and test power (1-β) of 0.3. Therefore, a sample size of 17 patients per group was calculated, yet 21 patients were selected in each group, predicting that there would be 12% dropout during the study. Thus, 42 individuals were selected for ECT among the patients.

Before starting the study, complete explanation about the intervention, possible side effects, and patient's autonomy was conducted for all cases, individually, leaving the option of exiting the study whenever they wanted. Moreover, written formal consent form was signed by the patients or their legal guardians in accordance with the Declaration of Helsinki. All treatments were offered to the patients at no expense. The ethics committee of Shahid Beheshti University of Medical Sciences (No. 9169) approved the study and it was registered at the Iranian Center of Clinical Trial Registration with ID number of IRCT 2016060628309N1.

The researchers randomly assigned patients (1:1) to either naltrexone or placebo by an automated system. Randomization of patients in groups A (Naltrexone) and B (placebo) was done by a random number generator. Participants, study team, and staff were masked to treatment allocation. Active drug and placebo tablets were identical in appearance. To ensure masking, only the corresponding psychiatrist was aware of the content of drug capsules and a trained psychiatry resident performed the counseling and data collection.

Patients received 6 sessions of ECT within 2 weeks (three times a week) after assignment to the study and underwent 6 sessions of bilateral frontotemporal ECT. The ECT was administered by Thymatron DGX device (Somatics, ILC, lake Bluff, USA). All ECT methods were administered between 7 and 9 A.M at Imam Hossein hospital. Patients were supposed to abstain from food at least 8 hours before the ECT procedure. At the first treatment, seizure threshold was used by the empirical titration procedure and in the subsequent sessions, stimulus intensity was maintained at 50% to 100% above the initial seizure threshold. Anesthetic agents included propofol (AstraZeneca, England) at an average dose of 0.5 to 1 mg/kg, succinylcholine (Caspain, Iran) 20 mg and atropine (Alborzdaru, Iran) 0.5 mg. Seizure duration was inscripted by isolation of one leg by inflation of cuff over 240 mmHg to assess quality of seizure as well as visual monitoring of residual motor convulsive activity. If the seizure durations were less than 15 seconds, 50% increase would be applied on the electrical dose. Vital signs were examined prior to and during the 5-minute period following seizure termination. A bag and mask of 100% oxygen was used to support the patients'

ventilation till the patients' breath resumed.

On the afternoon before each ECT session (approximately 12 hours), one capsule of naltrexone (50 mg) or placebo (resembling exactly similar to naltrexone in color and shape) was consumed by each patient. Thus, in total 6 capsules were used by patients in each group. The dose of naltrexone was chosen according to availability of 50 mg capsule in Iran. Drug compliance was measured by the report of head nurses (inpatients) or family members (outpatients).

With a face-to-face interview by a psychiatric resident, which took place one day before the first ECT session, Wechsler memory scale (WMS) and Hamilton depression rating scale (HDRS) were performed. After all 6 ECT sessions, WMS was performed 3 more times (approximately at 2 weeks, 1 and 3 months later). Furthermore, HDRS was also repeated 3 months later with the last WMS. Participant assessments were undertaken on the day before the first session of ECT, in addition to 2 weeks, 1 and 3 months after finishing the 6th session.

Depression was assessed by a trained psychologist, who was blinded to treatment assignment, using the HDRS one day prior to the first ECT session and 3 months after the final ECT. The researchers performed the test to examine the possible interference caused by depression or to relapse as a confounding variable.

Safety was assessed by daily evaluation of treatment emergent adverse events, characterized by good clinical practice guidelines. Concomitant medications, vital signs, baseline, and endpoint electrocardiographs were measured along with depressive symptoms (including suicidality, sadness, irritability, tension, and anxiety), in daily visits by a psychiatrist. Also, blood pressure was considered for efficacy and safety.

3.1. Measurements

3.1.1. Wechsler Memory Scale-Revised (WMS-R)

The WMS was designed in 1970 (19). The Revised WMS (WMS-R) includes 5 subscales (general memory, attention/concentration, verbal memory, visual memory, and delayed recall) and assesses various aspects of memory (20). Psychometric characteristics of the Farsi version of WMS-R was evaluated in Iran, on people aged 16 to 64 years. The reliability and validity of the scale was satisfactory (21).

3.1.2. Hamilton Depression Rating Scale (HRSD)

The HRSD is one of the most dependable scales in depression assessment. It is an instrument for a semi-structured interview based on DSM-VI criteria and it must be performed by a trained professional (22). The HRSD characterizes the symptoms of cognitive and physical signs of depression, depressed mood, and signs and symptoms of anxiety. It consists of 17 items along with a Likert scale of five (0 - 4) or three (0 - 2). It has a cut-off point of 13 (9).

Normal distribution of data was tested with Kolmogorov-Smirnov test and Q-Q graph. In order to compare the results among 2 groups for normal variables, t test was performed as well as Mann-Whitney test for variables without normal distributions or ranking. For assessment of qualitative variables, the Chi-Square test was used. Finally, to omit the possible effect of depression recurrence on memory tests, the researchers used analysis of covariance (ANCOVA) or covariance test. All analyses were performed by SPSS 21.0 and a P value of less than 0.05 was regarded as significant.

4. Results

Forty-two patients were included at the start of the study, yet 5 of them were omitted due to satisfaction of the exclusion criteria or their will to exit. Three of the mentioned patients were receiving naltrexone and 2 were being supplied by placebo.

As a result, primary assessment was done on 42 patients, however final conclusions were made based on 37 patients, 19 of whom received the placebo and 18 received naltrexone (Figure 1).

In primary evaluations and equalization among 42 patients, 20 were male and 22 were female. Mean age was 37.8 $\pm$ 11.8 years (range of 18 to 60). Seventeen cases had under diploma education and 15 and 10 patients had diploma and above, respectively. Mean score for HDRS in patients was 30.2 $\pm$ 7.5, indicating severe depression in the test. Based on obtained equalized results, data were observed in both naltrexone and placebo groups (Table 1).

Overall, mean age-adjusted score in WMS was 93.9 $\pm$ 10.4. There was no significant difference between naltrexone and placebo groups. This equality was observed in all 7 fields of WMS (Table 2).

After statistical evaluations of follow up scores (2 weeks, 1 month, and also 3 months), final score of WMS, which was age-adjusted and also memory quotient was not significantly different between the 2 groups. However, in the evaluation that compared baseline and follow up scores, the difference at 2 weeks after ECT in relation to baseline score was less in the naltrexone group than the placebo group. This difference was witnessed in all 3 cases of final scores of WMS (P = 0.04), age-adjusted score (P = 0.037), and memory quotient (P = 0.049). Data are presented in Tables 3 to 5.

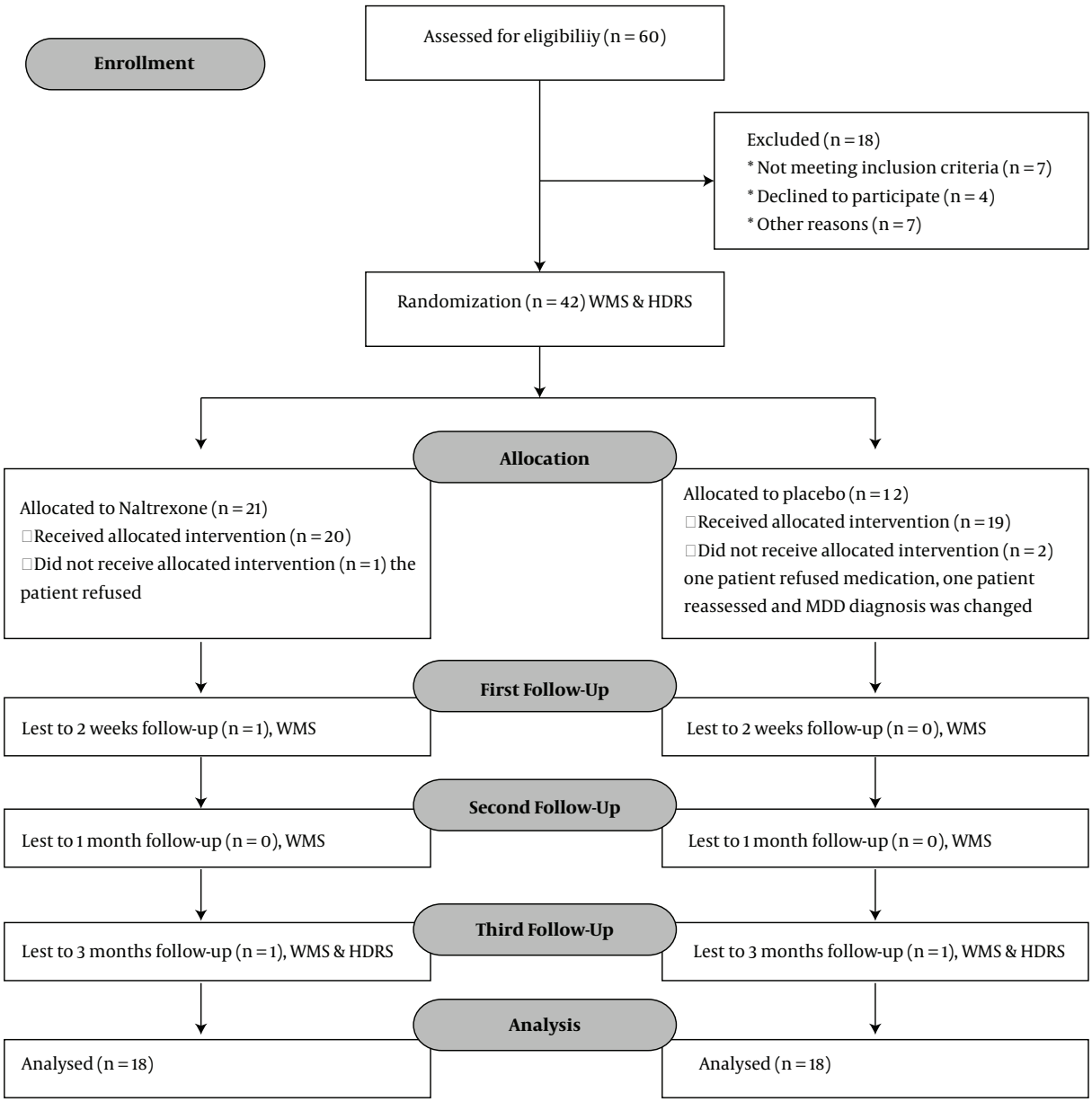

Figure 1. Intervention Scheme/Trial Flow Diagram

5. Discussion

The present study assessed the impact of 50 mg of naltrexone in reducing memory disorder after ECT and using WMS, moreover, changes at 3 different stages were tracked. Results demonstrated that after 2 weeks, 1 month, and 3 months, there were no significant differences between naltrexone and placebo groups. After further assessment, changes of WMS in every round at the 3 different times were compared. The later evaluation showed lesser memory reduction after 2 weeks in the naltrexone group in comparison with the placebo group.

Paradoxical results have been reported in limited previous studies. In one study designed to assess impact of naloxone on cognitive tests in 10 ECT patients, no difference was witnessed in naloxone and placebo groups. Although a major defect in the study was administration of naloxone after ECT, the authors mentioned low dose of the drug as a possible explanation (8). The authors hypoth-

Table 1. Baseline Characteristics of Patients

		Total	Placebo	Naltrexone	P Value
Age	Mean ± SD	37.8 ± 11.8	38.6 ± 10.4	37 ± 13.3	0.663[a]
	Median (range)	35 (18 to 60)	38 (18 to 59)	34 (20 to 60)	
Gender	M	20 (47.6)	10 (47.6)	10 (47.6)	1[b]
	F	22 (52.4)	11 (52.4)	11 (52.4)	
Education	< 12	17 (40.5)	6 (28.6)	11 (52.4)	0.158[c]
	12	15 (35.7)	9 (42.9)	6 (28.6)	
	> 12	10 (23.8)	6 (28.6)	4 (19.0)	
HDRS	Mean ± SD	30.2 ± 7.5	29.6 ± 6.5	30.7 ± 6.8	0.595[a]
	Median (range)	30 (18 to 44)	29 (18 to 42)	31 (22 to 44)	

[a] Based on t-test.
[b] Based on Chi-Square test.
[c] Based on Mann-Whitney test.

Table 2. Baseline Scores of Wechsler Memory Scale

		Total	Placebo	Naltrexone	P Value
General cognitive screener	Mean ± SD	5.2 ± 0.9	5.2 ± 0.9	5.1 ± 1	0.849[a]
	Median (range)	5 (3 to 6)	5 (3 to 6)	5 (3 to 6)	
Information and orientation	Mean ± SD	4.5 ± 0.7	4.5 ± 0.7	4.5 ± 0.8	0.801[a]
	Median (range)	5 (2 to 5)	5 (3 to 5)	5 (2 to 5)	
Mind control	Mean ± SD	7.6 ± 1.6	7.8 ± 1.5	7.4 ± 1.7	0.352[a]
	Median (range)	8 (3 to 9)	8 (4 to 9)	8 (3 to 9)	
Logical memory	Mean ± SD	5.3 ± 3.3	5.7 ± 3.8	5 ± 2.9	0.524[b]
	Median (range)	5 (0 to 15)	6 (0 to 15)	4 (0 to 12)	
Digit span	Mean ± SD	8.3 ± 2.5	8.7 ± 2.6	8 ± 2.5	0.369[b]
	Median (range)	8.5 (4 to 13)	9 (4 to 13)	8 (4 to 12)	
Visual reproduction	Mean ± SD	8.9 ± 3.9	8.8 ± 3.8	9 ± 4.2	0.848[b]
	Median (range)	10 (0 to 14)	8 (2 to 13)	10 (0 to 14)	
Verbal paired association	Mean ± SD	16.2 ± 2.7	16.1 ± 2.9	16.3 ± 2.5	0.776[b]
	Median (range)	16 (10 to 21)	17 (10 to 21)	16 (13 to 20)	
Total score	Mean ± SD	55.8 ± 11.8	56.2 ± 12.5	55.3 ± 11.4	0.807[b]
	Median (range)	58 (30 to 82)	59 (30 to 82)	57 (33 to 72)	
Age adjusted score	Mean ± SD	93.9 ± 10.4	95.1 ± 11.4	92.7 ± 9.3	0.464[b]
	Median (range)	96 (74 to 118)	96 (74 to 118)	94 (74 to 105)	
Quotient	Mean ± SD	94.9 ± 16.2	97.1 ± 18.4	92.7 ± 13.7	0.387[b]
	Median (range)	97 (66 to 143)	97 (66 to 143)	94 (66 to 112)	

[a] Based on Mann-Whitney test.
[b] Based on t-test.

esized that due to naltrexone half-life, its administration could prevent opioid neuropeptides release after ECT (23). Another group of researchers recognized the positive effect of high dose of naloxone only in a few antegrade memory determinants, including “verbal influency” and task performance in “total cancellation accuracy” test. The ob-

Table 3. Age-Adjusted Scores of Wechsler Memory Scale

Time		Total		Placebo		Naltrexone		P
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
Baseline	Value	55.8 ± 11.8	58 (30 to 82)	56.2 ± 12.5	59 (30 to 82)	55.3 ± 11.4	57 (33 to 72)	0.890
Week 2	Value	54.6 ± 12.1	57 (28 to 76)	53.1 ± 11.8	56 (28 to 76)	56.1 ± 12.5	59 (30 to 74)	0.392
	Change from Base	-1.2 ± 3.1	-1 (-7 to 5)	-2.3 ± 3.1	-2.5 (-7 to 4)	-0.2 ± 2.8	0 (-5 to 5)	0.040[a]
Month 1	Value	59.6 ± 11.3	60.5 (35 to 80)	58.4 ± 9.5	57 (47 to 80)	60.8 ± 13.1	64.5 (35 to 77)	0.428
	Change from Base	2.8 ± 4.9	2 (-8 to 13)	2.4 ± 4.6	2 (-3 to 13)	3.1 ± 5.3	2 (-8 to 13)	0.571
	Change from W2	3.6 ± 4.3	3 (-5 to 15)	4.2 ± 3.7	3 (0 to 12)	3.1 ± 4.9	3.5 (-5 to 15)	0.677
Month 3	Value	60.8 ± 13.2	63 (29 to 83)	60.1 ± 11.9	61 (29 to 81)	61.4 ± 14.8	65.5 (30 to 83)	0.533
	Change from Base	4.7 ± 5.5	3 (-4 to 15)	4.3 ± 4.9	3 (-1 to 15)	5.2 ± 6.2	4 (-4 to 14)	0.831
	Change from W2	44.8 ± 11.2	45.5 (18 to 63)	44.7 ± 9.9	45 (19 to 62)	44.9 ± 12.8	50.5 (18 to 63)	0.646

[a] $P < 0.05$.

Table 4. HDRS Adjusted Scores of Wechsler Memory Scale

Time		Total		Placebo		Naltrexone		P Value
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
Baseline	Value	93.9 ± 10.4	96 (74 to 118)	95.1 ± 11.4	96 (74 to 118)	92.7 ± 9.3	94 (74 to 105)	0.537
Week 2	Value	92.4 ± 10.3	92 (72 to 112)	92.1 ± 11.2	91 (72 to 112)	92.8 ± 9.7	94.5 (72 to 108)	0.874
	Change from Base	-1.4 ± 3.2	-1 (-7 to 5)	-2.4 ± 3.2	-2.5 (-7 to 4)	-0.3 ± 2.8	-0.5 (-5 to 5)	0.037[a]
Month 1	Value	97.4 ± 10	97 (78 to 117)	97.7 ± 9.6	96.5 (85 to 116)	97.2 ± 10.6	98.5 (78 to 117)	0.955
	Change from Base	2.6 ± 4.9	2 (-8 to 13)	2.3 ± 4.8	2 (-5 to 13)	2.9 ± 5.2	2 (-8 to 13)	0.583
	Change from W2	3.6 ± 4.3	3 (-5 to 15)	4.3 ± 3.8	3 (0 to 12)	3.1 ± 4.9	3.5 (-5 to 15)	0.634
Month 3	Value	98.6 ± 11.4	100 (72 to 118)	99.1 ± 10.9	100 (73 to 117)	98.2 ± 12.1	99 (72 to 118)	0.773
	Change from Base	4.7 ± 5.4	3 (-4 to 15)	4.3 ± 4.9	3 (-1 to 15)	5.1 ± 6	4 (-4 to 14)	0.831
	Change from W2	43.8 ± 7	43 (30 to 59)	45.6 ± 5.7	44 (38 to 59)	42.1 ± 7.9	42.5 (30 to 57)	0.216

[a] $P < 0.05$.

tained results showed that high dose of naloxone is fruitless in retrograde memory tests, even leaving a negative trace in "shape stimuli" test evaluation (17).

There were studies in which the effect of opioid agonists was investigated. On the other hand, there have been studies, which showed that activation of endogenous opioid system following ECT has been strongly demonstrated. Beta-endorphins and met-enkephalins release can lead to retro/antegrade memory dysfunction. Ability of naloxone as an opioid receptor antagonist has been discussed in animal studies (23, 24). Also, human studies based on the ability of naloxone have been leading to paradoxical results (17, 25).

Despite the difference of antagonist agents used in the current study compared to previous researchers and also memory evaluation tools, it seems that results of the present study have compatibility with previous reports to some degree. Impact of naltrexone in the final WMS (sum of sub-test scores), age-adjusted final score and quotient of memory, and also "verbal paired association" after 2 weeks is now proved by the current study. This impact could be considered similar to the impact of naloxone in improvement of antegrade memory.

Until now, paradoxical and different studies have been conducted on animal and human samples upon factors capable of reducing cognitive side effects and memory deficit followed by ECT (8, 26-30). However, these studies were limited in the level of human samples. An animal study investigating the molecular mechanism and propofol effect on rats' memory revealed that propo-

Table 5. Memory Quotient After Adjustment for Hamilton Depression Rating Scale

Time		Total		Placebo		Naltrexone		P Value
		Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
Baseline	Value	94.9 ± 16.2	97 (66 to 143)	97.1 ± 18.4	97 (66 to 143)	92.7 ± 13.7	94 (66 to 112)	0.537
Week 2	Value	92.8 ± 15.5	91.5 (64 to 126)	92.4 ± 17.2	90 (64 to 126)	93.1 ± 14.2	95 (64 to 118)	0.874
	Change from Base	-2.1 ± 5.5	-2 (-17 to 10)	-4 ± 5.7	-3.5 (-17 to 6)	-0.1 ± 4.6	-0.5 (-8 to 10)	0.049[a]
Month 1	Value	100.9 ± 16.9	99 (72 to 140)	101.2 ± 16.5	98 (81 to 137)	100.6 ± 17.8	101 (72 to 140)	0.955
	Change from Base	4.6 ± 8.4	3.5 (-11 to 30)	3.4 ± 7	3.5 (-7 to 18)	5.7 ± 9.7	3.5 (-11 to 30)	0.558
	Change from W2	6.2 ± 7.9	6 (-7 to 34)	6.8 ± 6	5 (0 to 18)	5.6 ± 9.5	6 (-7 to 34)	0.621
Month 3	Value	103.1 ± 19.1	103 (64 to 143)	103.6 ± 18.2	103 (65 to 140)	102.7 ± 20.6	101.5 (64 to 143)	0.773
	Change from Base	8.1 ± 9.4	6 (-5 to 33)	6.9 ± 7.2	6 (-3 to 21)	9.4 ± 11.3	7.5 (-5 to 33)	0.761
	Change from W2	10.4 ± 11.4	10 (-8 to 41)	10.9 ± 9.3	12 (-7 to 28)	9.8 ± 13.5	10 (-8 to 41)	0.557

[a] $P < 0.05$.

fol soothed electroconvulsive shock-induced learning-memory impairment without interfering with the antidepressant efficacy of ECS, possibly by inhibiting excessive expression of GAD65 and maintaining the balance between glutamatergic and GABAergic amino acids neurotransmitters in the hippocampus (31). Some other studies also examined the role of Anastasia agents of choice in improving cognitive function in human subjects and their early results suggest that agents, such as ketamine, may have particular benefits (32). In a study by Rezaei et al. (33), by adding remifentanil to propofol, immediate cognitive adverse effects turned out to be significantly lower in remifentanil group after ECT.

Based on previous studies, effect of ECT in memory dysfunction in depressed patients was shown to be independent of the impact of depression on memory loss itself (34). Nevertheless, the current research performed HDRS both before ECT to equalize the 2 groups and also 3 months after the last ECT session. After 3 months, recurrence of depression was observed in patients of both groups by HDRS, therefore statistical analysis was performed in such a way that effect of intervening depression on WMS scores was omitted by appropriate correction.

The results of this study suggest that despite the proven documents about the relationship of opioid system with memory function, 50 mg of naltrexone could not significantly improve the effect of ECT in memory dysfunction in patients with depression. However, it could be suggested that 2 weeks after ECT, as comparison to placebo, 50 mg of naltrexone has lower reduction rate in the amount of memory score from baseline. Therefore, the drug may be used in short periods since it indicated no positive effect during longer periods.

The study was associated with some limitations. One of them was the lack of sufficient background data on dosing of naltrexone, which could alter the results. Another impediment of the study was downfall of a few patients. This was accompanied by 2 cases of a lack of cooperation for the follow up phase. One major limitation was that due to possibility of recurrence of depression and its impact on memory test, the researchers performed HDRS 3 months after ECT, yet the test was not performed during the early days and weeks. Therefore, lack of patient's cooperation may have been due to recurrence of depression sooner than expected.

The authors suggest that evaluation of the effect of naltrexone at different doses may be useful for future studies. Comparison of naltrexone with naloxone requires further attention. Also, different sub-tests and antegrade and retrograde types of memory could be subject of future evaluations.

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Footnotes

Authors' Contribution: Somayeh Motazedian, Alireza Zahiroddin, and Simasadat Noorbakhsh: study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and drafting of the manuscript. Jamal Shams and Reyhaneh Jafari,

and Mohamadmahdi Faghihimohamadi: assistance in acquisition of data and all experiments, especially in medical consultation, administrative, technical, and material support, assistance in the study design, and study supervision.

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