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Safety of Electro-Convulsive Therapy in Combination with Duloxetine in Treatment-resistant Depressive Patients: A Randomized Clinical Trial

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Abstract

Background: There are several strategies in the management of treatment-resistant depression (TRD), including the administration of other antidepressants, augmentation therapy, electro-convulsive therapy (ECT), and a combination of ECT and antidepressants. The safety of ECT combined with any medication must be confirmed. The aim of this study was to assess the safety of duloxetine and ECT combination therapy. **Materials and Methods:** In this randomized clinical trial, the probable side effects of ECT plus duloxetine were compared with ECT plus sertraline in two groups of admitted TRD patients. Patients with general medical diseases and/or any contraindications to ECT or any of the two drugs were excluded. General side effects, including nausea, vomiting, and headache reported by patients (hours after ECT) as well as cardiotoxicity by electrocardiogram (immediately after any ECT episode), cognitive status by mini-mental state examination (MMSE, one month after the last ECT), and seizure duration were recorded for each patient. **Results:** No significant differences were observed in nausea, vomiting, headache, and myalgia between ECT+duloxetine and ECT+sertraline groups. Heart rate, QTc interval, ST-T change, and the incidence of arrhythmia were the same between the two arms of the study. Also, no prolonged seizures and status epilepticus were recorded among the studied patients. The MMSE revealed no marked differences in the cognitive status among patients of the two groups. **Conclusion:** ECT+duloxetine and ECT+sertraline were equally safe in patients with TRD.

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Keywords: Depressive Disorder; Duloxetine; Electro-convulsive Therapy; Sertraline; Cardiotoxicity

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Introduction

Treatment-resistant depression (TRD) is defined as a major depressive mood state without response to two or more antidepressant therapy with full doses and adequate administration duration [1]. It has been reported that 2 to 46% of depressed patients do not respond to antidepressant pharmacotherapy [2]. TRD patients experience worse outcomes compared to other depressed patients. This poor prognosis mental condition can increase the risk of suicide two- or three-fold compared to patients who respond to treatments. There are several therapeutic modalities for TRD, e.g., augmentation of antidepressant pharmacotherapy with atypical antipsychotic drugs, psychostimulants, and neurostimulation [3, 4].

Electro-convulsive therapy (ECT) has emerged as a modality for TRD since 1938 [5]. ECT is used 6 to 12 times (2 to 3 sessions per week) for patients with TRD, and 50 to 80 % get remission after an ECT course. Evidence has shown ECT to be tolerable and safe [5]. However, side effects such as cardiac disorders, prolonged seizures, and persistent cognitive impairment are reported after ECT [6]. The emergence of new antidepressants has provided new modalities for the pharmacological treatment of TRD.

On the other hand, among modern antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs) have been extensively used to treat the major depressive disorder (MDD). It has been strongly suggested that SNRIs, including duloxetine, are effective in TRD [7, 8]. Nevertheless, some patients respond poorly to novel antidepressants and ultimately need ECT therapy. These patients are obviously accounted as TRD. Previous studies indicated that the combination of some SNRIs and ECT could be beneficial for the induction of remission in significant TRD patients; however, more clinical trials are needed to establish the safety of this combination [9]. Pinto *et al.* reported that a combination of SNRIs (i.e., venlafaxine, 300 mg) with ECT was safe and effective in TRD [10]. In higher doses of venlafaxine, some cases experienced asystole [10]. Duloxetine, a relatively new SNRI, is effective with doses of 40 to 120 mg daily and can alleviate symptoms of depression. The safety of the combination of ECT with duloxetine has been only reported as case reports, and there is no clinical trial published in the literature to evaluate this combination regarding safety [11]. Toxicities of the combination of other antidepressants and ECT have been reported. For instance, lengthening of seizure time has been reported in combination therapy with bupropion and ECT [12].

Moreover, the cognitive adverse effects of some antidepressants in combination with ECT are of concern. These side effects, as well as other probable toxicities, have never been studied for the combination of duloxetine and ECT. In our previous study, we evaluated the behavioral markers, cardiovascular function, and brain oxidative stress markers in mice that received duloxetine and ECT and suggested that the administration of this combination in the mouse model was safe [12].

Also, sertraline is a selective serotonin reuptake inhibitor (SSRI), and its combination with ECT has been previously shown to be relatively safe [13]. Hence, we aimed to compare the side effect profile of ECT plus duloxetine versus ECT plus sertraline.

Materials and Methods

This phase three randomized clinical trial was conducted in Ibn Sina Psychiatry hospital, a subsidiary training and research psychiatric diseases center of Shiraz University of medical sciences.

Ethical Considerations

Our study protocol was approved by the ethical committee of Shiraz University of Medical Sciences (ethical code: IR.SUMS.MED.REC.1396.60). Also, this study was registered in the Iranian registry of clinical trials (code: IRCT20181204041847N1). Written informed constants were obtained from patients, and all the data was kept confidential.

Sample Size Calculation

The sample size of the current study was

determined based on regarding Gonzalez-Pinto *et al*. [10] study.

Inclusion and Exclusion Criteria

Patients aged 20 to 60 years old and diagnosed with TRD were enrolled. Also, patients diagnosed with cardiovascular, neurologic, or other general medical conditions, any contraindication for ECT application, using other antidepressants and/or medications with a possible effect on ECT toxicity were excluded from the study.

Randomization

In this study, patients were assigned to duloxetine and sertraline groups by block randomization method. In order to perform randomization, six blocks of four were designed as follows. They were placed separately in sealed envelopes. Then, eight times one block with the placement was chosen randomly. The sequence implanted in each block determined the status of the following four patients.

Design and Data Collection

Design and Data Collection

Patients were allocated into duloxetine (60-120 mg, mean=66.25 mg, Kishmedifarm, Iran) +ECT group was compared with sertraline (50-300 mg, mean=94.11 mg, Abidi, Iran) +ECT. The medication doses were not changed in the last week before starting and during the ECT. No patients received any medication that induced prolonged QTc or heart rate (HR) change. Before ECT, propofol (60 mg) and succinylcholine (40 mg) were administered as the same anesthetic protocol for all the patients [14, 15]. No patients needed to receive atropine. In the duloxetine group, the patients were treated with bilateral ECT (voltage adjusted according to the age, 6-12 sessions based on the response of the patient) [16]. In the second group, TRD patients received sertraline plus ECT. Electrocardiography (baseline and immediately after each ECT episode), duration of each convulsion time, cognitive status, headache, and nausea/vomiting were recorded. For the cognitive scoring scale, the mini-mental status examination (MMSE) questionnaire was administered by a psychiatrist before and one month after the end of the ECT treatment course [17]. The metabolic state (lipid profile and blood sugar), type and dose of anesthetic agent, and any consumed supplement were also recorded.

Statistical Analysis

All data were analyzed using SPSS version 16 (SPSS Inc., Chicago IL, USA). All side effects between the two groups were compared using the Chi-square test. Also, the duration of seizures was compared using t-test in each arm. The significance levels were set as P-value<0.05.

Results

Among 45 eligible patients, 37 patients were entered into the study. Then, 18 and 19 patients were allocated to duloxetine and sertraline groups, respectively (Figure-1). Finally, two patients in the duloxetine group were lost during one month of follow-up. Also, two patients in the sertraline group discontinued treatment.

The mean age of patients in the duloxetine and sertraline groups was 38.92±12.09 and 39.18±13.17 years, respectively. Five patients in each group were male. There were no any significant differences between duloxetine and sertraline groups in terms of sex and age (P>0.05).

General Side Effects and Electrocardiograph Changes

Table-1 shows no significant differences in the presentation of general side effects between the sertraline+ECT and duloxetine+ECT groups. The changes in the electrocardiograph of both groups were the same, including arrhythmias, ST-T change, QTc prolongation, and HR alterations before and at three sequential ECT (Table-1).

Duration of Convulsion and Cognitive Status of Patients

Our results demonstrated that neither of the groups had status epilepticus and all the

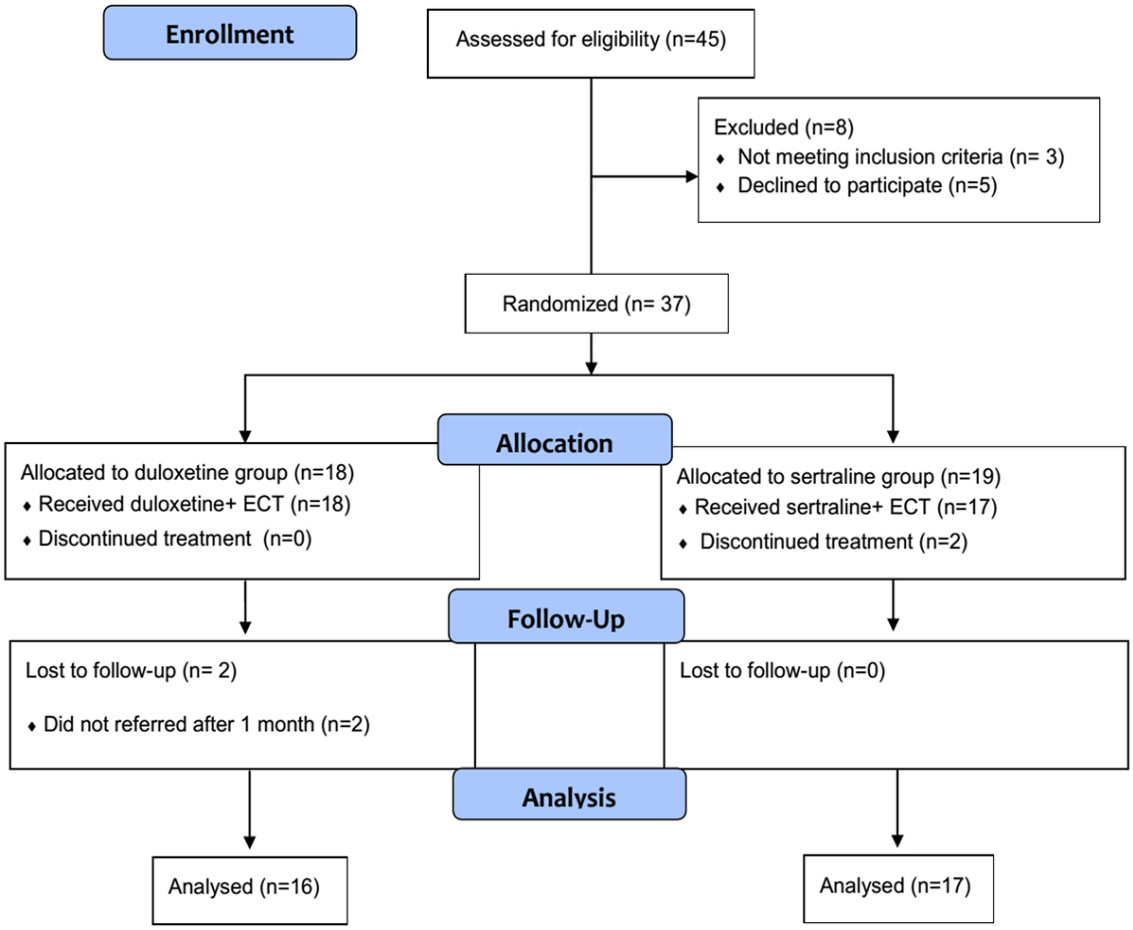

Figure 1. CONSORT flow diagram of study

convulsions stopped spontaneously at the standard time after each ECT episode. The differences between both groups regarding the duration of seizures after ECTs were the same (Table-1).

Based on MMSE results, there were no differences between the cognitive status of the patients in either group of duloxetine and sertraline at the baseline (Table-1, P=0.25). Also, no statistically significant differences were observed between the groups one month after ECT (Table-1, P=0.469).

Discussion

The ECT is older than pharmacotherapy for treating psychiatric disorders, including TRD [1, 16]. As a result, we can face many interactions between the effect of medications and ECT [16]. So, there should be evidence that the combination of two completely different treatments is both safe and effective in terms of the treatment of psychiatric disorders.

SSRIs seem to have a safer cardiological profile than many other antidepressants when they are augmented with ECT as a control medication [18]. On the other hand, SNRIs are among the newest generations of antidepressants mainly used for TRD patients. One of these very important and commonly consumed medications is duloxetine, which is widely used for neuropathic pain associated with diabetic peripheral neuropathy, generalized anxiety disorder, fibromyalgia, chronic musculoskeletal pain, etc. [19]. Duloxetine is a state-of-the-art antidepressant of the SNRIs group commonly administered for TRD [7]. There are many concerns about the old SNRIs; venlafaxine, a popular antidepressant, combined with ECT, because of the cardiac sinus pause and sinus arrest reported when it is used at higher doses [10].

We have suggested that the combination of duloxetine+ECT is as safe as sertraline+ECT

Table 1. Frequency of General Side Effects, Cardiotoxicity, and MMSE Score of Studied Patients

Variables	Groups		P-value
	Duloxetine+ECT	Serteraline+ECT	
Nausea, n(%)	5 (31.3)	3 (17.6)	0.531
Vomiting, n(%)	2 (12.5)	2 (11.8)	0.568
Headache, n(%)	9 (56.3)	9 (55.2)	0.131
Myalgia, n(%)	3 (18.8)	2 (11.8)	0.226
Arrhythmia, n(%)	2 (12.5)	2 (11.8)	0.948
ST-T wave changes, n(%)	2 (12.5)	2 (11.8)	0.948
HR changes, minutes (mean±SD)			
HR 1-HR 0	4.31±14.56	5.47 ±11.69	0.802
HR 2-HR 0	2.25±18.53	3.23±14.79	0.867
HR 3-HR 0	12±13.62	6.47±16.4	0.238
QTc change, (mean±SD)			
QTc 1-QTc 0	5.81±36.72	-10.7±31.44	0.174
QTc 2-QTc 0	0±42.39	-6.94±38.79	0.627
QTc 3-QTc 0	7.12±41.81	-0.64±36.83	0.574
MMSE score, (mean±SD)			
Baseline	26.25±3.27	27.47±2.69	0.25
One month	1.31±2.67	0.7±1.48	0.469

* HR and QTc were recorded after 1st, 2nd and 3rd ECT
HR: Heart rate; **ECT**: Electro-convulsive therapy; **MMSE**: Mini-mental state examination

[18]. The tolerability of the latter has been practically accepted. Regarding our findings, there were no differences between the general side effects of ECT after the dose of duloxetine therapy in TRD patients, including nausea, vomiting, headache, and myalgia, compared with sertraline+ECT. General side effects such as nausea, headache, and dizziness were reported in the combination of ECT plus venlafaxine and paroxetine, fluvoxamine, citalopram, amitriptyline, clomipramine, fluoxetine, and mirtazapine [20].

There are some lines of evidence regarding the possibility of arrhythmogenicity of the combination of ECT and some antidepressants, such as tricyclic antidepressants and trazodone [21]. Although no arrhythmia was found among the patients of the duloxetine group in our study, there was a case report regarding ventricular tachycardia after concomitant treatment with ECT+lithium+ duloxetine in a woman with the recurrent affective disorder [22]. Safety regarding the cardiac rhythm is very important because venlafaxine has been reported to cause sinus arrest when administered at high doses before ECT [10]. However, administration of regular doses of duloxetine did not make any of this sometimes-troublesome sinus pause.

Also, in the current study, no prolongation in QTc means that both combined regimens probably lack the risk of arrhythmogenicity. No significant ST-T changes were observed in either of the groups. It can be concluded that safety regarding ischemic change for duloxetine when followed by ECT. No changes in HR are comparatively different between the two groups.

Also, the cognition was examined by MMSE before and one month after ECT [17]. In comparison with the sertraline group, the patients in the duloxetine group do not have any significant decrease in cognition based on the MMSE test. lisanby *et al*. reported the safe neurocognitive profile of ECT+venlafaxine+lithium used in both acute and continuation phases treated by ECT after remission [23]. On the other hand,

Sakiem *et al*. mentioned that venlafaxine, combined with ECT, aggravates the cognition side effects c ompared t o nortriptyline+ECT [24]. Status epilepticus and prolonged seizures (more than three minutes) are the main concerns after induction of seizure by ECT, which place in 1 to 2 % of seizures induced by ECT [25]. In the current study, no prolonged seizure with the combination of ECT and duloxetine was observed. Paroxetine, fluvoxamine, trazodone, tricyclic antidepressants, and especially bupropion have been reported to decrease the threshold of seizure and might prolong seizure time [21, 26].

Ultimately, we can provide some strong evidence that the combination of duloxetine and ECT is at least as safe as the combination of sertraline and ECT. Eraslan *et al*. reported two patients with suicidal ideas and psychotic features which were treated with duloxetine (30 mg) and ECT successfully without any important complications [11]. A report from Heinz *et al*. has shown postictal ventricular tachycardia after co-administration of ECT with duloxetine and lithium [22]. In another case report, ECT plus duloxetine and olanzapine was tolerated without any complication in MDD patients [27]. Although in our study we did not increase the dose of duloxetine (due to ethical issues), we suggest that the previously reported sinus pauses of venlafaxine do not considered as complications of SNRIs.

There are some limitations in the current study. The maximum doses of medications (duloxetine and sertraline) were administered in a few patients due to the intolerance of most patients. Also, other neurocognitive tests, including the Wechsler Memory Scale, could be applied for better evaluation of memory loss in patients.

Further studies with larger sample sizes, and monitored drug blood levels with the highest doses (based on patients' tolerance) are recommended.

Conclusion

Duloxetine and sertraline were equally safe in the treatment of patients with TRD. Indeed, no significant side effects were observed in patients of the two groups.

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Conflict of Interest

The authors disclose that they have no conflict of interest.

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