Is the Ultimate Treatment Response Predictable with Early Response in Major Depressive Episode?

Aslı ÇİFTÇİ¹, Halis ULAŞ², Ahmet TOPUZOĞLU², Zeliha TUNCA³

¹Department of Psychiatry, Horasan State Hospital, Erzurum, Turkey

²Department of Psychiatry, Dokuz Eylül University School of Medicine, İzmir, Turkey

³Retired Lecturer, Department of Psychiatry, Dokuz Eylül University School of Medicine, İzmir, Turkey

ABSTRACT

Introduction: New evidence suggests that the efficacy of antidepressants occurs within the first weeks of treatment and this early response predicts the later response. The purpose of the present study was to investigate if the partial response in the first week predicts the response at the end of treatment in patients with major depressive disorder who are treated with either antidepressant medication or electroconvulsive therapy.

Methods: Inpatients from Dokuz Eylül University Hospital with a major depressive episode, treated with antidepressant medication (n=52) or electroconvulsive therapy (ECT) (n=48), were recruited for the study. The data were retrospectively collected to decide whether a 25% decrease in the Hamilton Depression Rating Scale (HDRS) score at the first week of treatment predicts a 50% decrease at the third week using validity analysis. In addition, the effects of socio-demographic and clinical variables on the treatment response were assessed.

Results: A 25% decrease in the HDRS score in the first week of treatment predicted a 50% decrease in the HDRS score in the third week with a 78.3% positive predictive value, 62.1% negative predictive value, 62.1% sensitivity, and 78.3% specificity for antidepressant medications and an 88% positive predictive value, 52.2% negative predictive value, 66.7% sensitivity, and 80% specificity for ECT. The number of previous hospitalizations, comorbid medical illnesses, number of depressive episodes, duration of illness, and duration of the current episode were related to the treatment response.

Conclusion: Treatment response in the first week predicted the response in the third week with a high specificity and a high positive predictive value. Close monitoring of the response from the first week of treatment may thus help the clinician to predict the subsequent response.

Keywords: Antidepressant medications, electroconvulsive therapy, major depressive disorder, response, prediction

INTRODUCTION

Major depressive disorder is a psychiatric disorder that has an onset in adolescence or early adulthood, is most commonly seen in women, may become chronic, can coexist with other psychiatric and physical illnesses, can result in severe disability, and has a high prevalence in the society (lifetime prevalence 10–15%, point prevalence 4.7%, and annual prevalence 3%) (1,2). Major depression disorder may lead to severe disability and burden besides its high prevalence in the society. For instance, in the Global Burden of Disease study conducted in 1990, major depressive disorder was ranked fifteenth among all other diseases and injuries in terms of its global burden; however, it was raised up to tenth in relation to recent population growth and the rise in the number of elderly according to a replicated study in 2010 (3).

The treatment of major depressive disorder is crucial considering that it causes disability in patients and a great societal burden. Although antidepressants are ranked as the first line of treatment, one-third of patients do not respond to treatment despite different antidepressant medications (4).

In the treatment of major depressive disorder, the duration of response is as important as unresponsiveness to treatment. In the current treatment guidelines, it is stated that to evaluate the treatment response, a definite time is required to wait. For example, while the Canadian Network for Mood and Anxiety Treatments reports that 2–4 weeks are required to evaluate the response to antidepressant treatment in adult major depressive disorder (5), in the Texas Depression Treatment Algorithm and Treatment Guideline for Major Depressive Disorder of American Psychiatry Association, the duration is suggested to be 4–8 weeks (6,7). Despite still being included in treatment guidelines, the opinion that the effectiveness of antidepressants comes up late appears to lose its validity with the increasing evidence for the opposing view. For instance, Nierenberg et al. found in a study they conducted with fluoxetine that more than half of the patients responded to treatment in 2 weeks (8). In addition, in a meta-analysis performed by Taylor et al. (9), the data from a 50 placebo-controlled study conducted in patients with the diagnosis of unipolar depression using selective serotonin reuptake inhibitors (SSRI), it was found out that recovery of the symptoms began in the first week.

Correspondence Address: Halis Ulaş, Dokuz Eylül Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, İzmir, Türkiye
E-mail: halisulas@yahoo.com

Received: 26.12.2014 **Accepted:** 12.05.2015

©Copyright 2016 by Turkish Association of Neuropsychiatry - Available online at www.noropskiyatrisivi.com

The question that arises after establishing the result that the response to antidepressant drugs becomes evident in the early period is the extent of the importance of the early response as a factor in predicting the later response. Stassen et al. investigated the fluctuation of response to treatment as a variant of time in major depressive disorder patients and reported that the patients who demonstrated a 20% decrease from the initial score Hamilton Depression Scale (HDS) score in the first two weeks of treatment also responded to the treatment (50% decrease in the HDS score) at the end of the study. In this study, it was reported that not responding to treatment in the early period was also indicative of late unresponsiveness (10). In a six-week randomized, placebo-controlled study conducted by Katz et al. (11) in 2004 with patients taking paroxetine, which is SSRI, and desipramine, which is a norepinephrine reuptake inhibitor and placebo, it was reported that with both drugs, the response observed in the first two weeks was correlated with treatment response observed at the end of six weeks. In a meta-analysis, 41 studies including 6562 patients with major depressive disorder diagnosis and comparing mirtazapine with another antidepressant or with a placebo, it was found out that the early response predicted the later stable response and remission with a sensitivity of 81% and 87%, respectively. Similarly, the negative predictive value, which indicates a lower recovery rate of patients who do not display any improvement in the second week, was found to be high (12).

In a single-blind, randomized, placebo-controlled study comparing two antidepressant combination (bupropion+escitalopram and venlafaxine+mirtazapine) and escitalopram+ placebo, it was stated that for the physician to decide on treatment, the positive and negative predictive values were more important than sensitivity and specificity and a negative predictive value of 75% was accepted as significant (13).

In another study, 131 inpatients were administered fixed doses of fluoxetine 20 mg/day and the predictability of the pattern of the response to the drug together with the early response, which was determined by the decrease in HDS scores in the first weeks on late response, was investigated. The percentage of change was estimated by subtracting the HDS scores, which were assessed each week for six treatment weeks, from the initial HDS scores. The stable response was defined as a 50% decrease in the HDS score. In the estimation of the HDS percentage rate of change that predicts responsiveness and unresponsiveness in the first weeks with the highest sensitivity and specificity, ROC curve was used, and it was reported that a decrease in HDS scores by 25% in the first week, 39% in the second week, 43% in the third week, and 50% in the fourth week predicted the response at the sixth week, which was also the end of the study, with a high sensitivity and specificity (14).

In the treatment of major depressive disorder, electroconvulsive therapy (ECT) is used efficiently along with antidepressant medication. In algorithms of the Treatment for Major Depressive Disorders, ECT is recommended to be used in patients who do not benefit from the use of two antidepressants at effective doses for a sufficient duration and after the options of lithium and thyroid hormone replacement have been considered. However, there are also some conditions in which ECT may be used as the first option: patients who have previously responded to ECT positively, patients resistant to other treatments, patients who have severe suicide risk and/or thoughts of homicide, patients refusing oral intake, and pregnant patients. The effectiveness of ECT is considered to be 80–90% in unipolar and bipolar depressive disorder (15). Although the high effectiveness of ECT is well-known, there are a limited number of studies investigating the time of onset of its effectiveness. In a study in which Rodger et al. (16) investigated the pattern of response to ECT treatment, the registers of 11 patients with a diagnosis of major depressive disorder were examined, and it was deter-

mined that in patients who were administered ECT with a mean frequency of 6.6, the observed improvement after the first three ECTs was six times more than the improvement in the rest of the treatment. It was reported that patients who displayed more prominent improvement in the first three ECTs had a higher probability of recovery at the end of treatment (16). In another study, 253 patients with major depressive disorder diagnosis were administered three ECTs per week, and 217 patients were able to complete the study. The stable response rate, which was defined as a 50% decrease in HDS score compared to the initial score, was found to be 79%, and the remission rate, which was defined as a decrement of HDS score under 10 points, was found to be 75%. It was determined that 34% of patients entered remission before the sixth ECT, 65% before the tenth or at the tenth ECT, and also that in more than 50%, a response was observed after the third ECT; thus, it was reported that ECT is a treatment option with a fast onset of effectiveness and high efficiency (17).

The aim of the present study was to investigate the predictive value of the partial response of patients with a diagnosis of major depressive disorder to antidepressant medication and ECT in the first week on the response likely to be observed at the end of the treatment.

METHODS

Sample

Patients who had received inpatient treatment from the Dokuz Eylül Hospital Psychiatry Clinic with a diagnosis of major depressive disorder between the dates of 01.01.2002 and 01.07.2011 participated in the study. Necessary data were obtained through the retrospective scanning of patient files. The study was ethically approved by the Non-Invasive Research Ethical Committee of Dokuz Eylül University Medical School.

In the present study, we included patients who were diagnosed with a major depressive disorder or recurrent depressive disorder during hospitalization, were aged between 18 and 65 years, were treated with only one antidepressant or ECT during hospitalization, had more than 20 days of hospitalization, and had a primary diagnosis of major depressive disorder or recurrent depressive disorder if there was a comorbidity.

We excluded patients who had bipolar disorder or any disorder from the psychosis spectrum, had any organic disorder that could explain their psychiatric symptoms, or used more than one psychotropic medicine (patients who took benzodiazepine or a low dose of trazodone or mianserin, which has a sedative side effect for sleep induction, were not excluded). Moreover, we excluded patients who took antidepressant treatment together with ECT or those whose antidepressant dosages were increased.

Measurement tools

Hamilton Depression Scale (HDS): The scale was developed by Hamilton in 1960 (18). HDS consists of 17 items and aims to evaluate the intensity of depression. The scale is rated by the interviewer. Turkish validity and reliability analysis of the scale was conducted by Akdemir et al. (19). In our clinic, the scale is regularly administered once a week in order to evaluate and monitor the intensity of depressive symptoms during the hospitalization of patients with major depressive disorder.

Mini Mental State Examination (MMSE): MMSE was developed by Folstein et al. (20) as a cognitive assessment tool that takes only a short time to administer. Validity and reliability analysis in Turkish were reported by Güngen et al. (21). It consists of 11 items of five main subscales, namely orientation, record memory, attention and calculation, recall, and language. The total score is evaluated out of 30.

ECT procedure

ECT-indicating patients were consulted by the Anesthesiology and Reanimation Department and examined in terms of anesthesia implementation. ECT was performed with the Thymatron System IV ECT tool (Somatics, Inc., Lake Bluff, IL, USA), three times a week, under anesthesia, and bilaterally. ECT flow dosage was designed as half of the patient's age at the beginning. The electrical charge average at the first ECT session was 211 ± 55 mC (milicoulomb) and at the last session was 407 ± 215 mC. Seizure duration was determined by two channeled electroencephalography. Above 20 seconds of seizure was regarded as effective, and the energy level was increased by 50% if an effective seizure duration could not be reached.

In ECT treatment, the average session number was 8.8 ± 2.6 and the average effective ECT number was 8.3 ± 2.5 . Before anesthesia, 0.5 mg intravenous atropine and propofol (1 mL/kg) as anesthetic and succinylcholine (0.5 mg/kg) as myorelaxant were administered.

Criteria for response to treatment

Early response to treatment was identified as a 25% decrease in HDS scores with respect to the initial scores after the first week of antidepressant or ECT treatment. On the other hand, late response to treatment was defined as a 50% decrease in HDS scores considering the initial scores at the third week of treatment. These descriptions are compatible with the Texas Depression Treatment Algorithm, which defines a decrease less than 25% as "no response," a decrease between 25 and 50% as a "minimal response," a decrease between 50 and 75% as a "partial response," and a decrease between 75 and 100% as a "complete response" (6).

Statistical Analysis

Statistical analysis of the data was produced using the Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 15.0. Validation analysis was used in order to evaluate the prediction of the early stage response on the late stage response. Accordingly, sensitivity, specificity, the negative prediction value, and the positive prediction value were calculated.

Response to treatment at the first week was defined as a 25% decrease in HDS scores compared to the initial score. In addition to this cutoff point, for the purpose of determining the cutoff point in which sensitivity and specificity are the highest and, accordingly, false negatives and false positives are the lowest, ROC analysis was conducted. For each cutoff point, the possibility of positivity and negativity were calculated.

Numbers and percentages for the descriptive data and the mean and standard deviation for the measured data were used in the analysis. For a pair-wise comparison of qualitative data, the chi-square and Fisher's absolute chi-square tests were run, whereas the Mann-Whitney U test was used for the pair-wise comparison of quantitative and non-normally distributed data. The significance range was accepted as <0.05 for statistical comparisons.

RESULTS

Socio-demographic and clinical characteristics of the antidepressant treatment and ECT groups

The antidepressant treatment group consisted of 52 (34 female, 18 male) patients, and the mean age was 40.7 ± 12.5 years. The ECT group consisted of 48 (34 female, 14 male) patients, and the mean age was 41.9 ± 13.6 years. Socio-demographic characteristics of the antidepressant and ECT groups are shown in Table 1. The two groups did not differ in terms of socio-demographical and clinical characteristics, except for marital status and the total number of hospitalizations. More single patients were present in the ECT group, and their number of hospitalizations was greater than in the antidepressant group.

The impact of socio-demographic and clinical characteristics on the response to treatment

The ECT and antidepressant groups were divided into subgroups in terms of a decrease in HDS scores by 25 % at the first week and by 50% at the third week, and they were compared with respect to their clinical and socio-demographic characteristics. Table 2 presents the comparison in terms of socio-demographic and clinical characteristics of ECT treatment patients with a decrease at the first week in HDS scores by 25% from the initial score and patients who did not show a decrease by 25%. The total number of hospitalizations was significantly lower in the patients who had a decrease in first-week HDS scores by 25% than for patients who did not show a 25% decrease ($p=0.02$). Current duration of the episode was approximately three times longer in patients without an early response to treatment compared to patients with an early response to treatment ($p=0.050$).

Comparison of the patients who showed a 25% decrease in HDS scores regarding the start of treatment and the patients who did not show a 25% decrease in the antidepressant treatment group in terms of socio-demographic and clinical characteristics is presented in Table 3. The total number of hospitalizations was significantly higher for patients who did not show a 25% decrease in HDS scores compared with those that did at the start of treatment ($p=0.01$). Besides attaining to the limit of statistical significance, the total number of episodes was higher; the age of disorder onset was earlier; and the duration of the current episode was longer for patients whose response to treatment in the first week was partial.

48% of the patients were taking SSRI, 32.7% of them were taking SNRI, 5.8% of them were taking tricyclic antidepressant, 5.8% of them were taking tetracyclic antidepressant, and 5.8% of them were taking NaSSA (mirtazapine).

The ECT and antidepressant treatment groups were divided into subgroups in terms of whether the patients showed a 50% decrease in HDS scores at the third week, which was the second assessment time. These subgroups were compared with respect to socio-demographic and clinical characteristics that were assessed at the first week assessment. Accordingly, the response to ECT treatment was not related to age, gender, marital status, years of education, work status, psychotic features, family history, presence and number of suicide attempts, or the Mini Mental State Examination scores that were assessed at the start. When the patients who did not show a 50% decrease in HDS scores at the third week were compared to the responsive patients, they showed a greater probability of having medical disorders ($p=0.028$), a greater total number of episodes ($p=0.036$), longer durations of disorder ($p=0.028$) and longer durations of the current episode ($p=0.041$), and a greater number of hospitalizations ($p=0.035$). Subgroups of the antidepressant treatment group, which were responsive and unresponsive to treatment at the third week, were not related with age, gender, marital status, work status, years of education, psychotic features, family history, suicide attempts, medical disorders, number of episodes, age of disorder onset, duration of disorder, number of hospitalizations, or the Mini Mental State Examination scores evaluated at the start. The comorbidity of another psychiatric diagnosis was found statistically higher in the patients who did not show a 50% decrease in the third-week HDS scores than for the responsive patients ($p=0.035$). Although reaching no statistical significance, the duration of the current episode was longer with the unresponsive patients.

Prediction of first-week treatment response of the third-week treatment response

Validation analysis indicated that the first-week treatment response can predict the third-week treatment response for patients using antidepressant treatment with 62.1% sensitivity, 78.3% specificity, a 78.3% positive predictive value (PPV), and a 62.1% negative predictive value (NPV). On

Table 1. Socio-demographic characteristics of the antidepressant and ECT groups

	Antidepressant treatment n=52	ECT n=48	
Age	40.7±12.5	41.9±13.6	Mann-Whitney U=1197.0 p=0.73
Years of education	10.6±3.4	11.2±4.6	Mann-Whitney U=1025.0 p=0.11
Gender			
Female	34/52 (65.4%)	34/48 (70.8%)	X ² =0.341 SD=1 p=0.56
Male	18/52 (34.6%)	14/48 (29.2%)	
Working status			
Working	27/52 (51.9%)	19/48 (36.9%)	X ² =1.5 SD=1 p=0.22
Not working	25/52 (48.1%)	29/48 (60.4%)	
Marital status			
Single	11/52 (21.2%)	14/48 (29.2%)	Fisher's Absolute X ² , p=0.04
Married	36/52 (69.2%)	22/48 (45.8%)	
Divorced	4/52 (7.7%)	5/52 (10.4%)	
Widow	1/52 (1.9%)	7/48 (14.6%)	
Psychotic features			
Present	5/52 (9.6%)	11/48 (22.9%)	X ² =3.3 SD=1 p=0.07
Absent	47/52 (90.4%)	37/48 (73.1%)	
Family history			
Present	18/52 (34.6%)	20/48 (41.7%)	X ² =0.5 SD=1 p=0.47
Absent	34/52 (65.4%)	28/48 (58.3%)	
Suicide attempts			
Present	25/52 (48.1%)	21/48 (43.8%)	X ² =0.2 SD=1 p=0.67
Absent	27/52 (51.9%)	27/48 (56.3%)	
Medical disorders			
Present	22/52 (42.3%)	16/48 (33.3%)	X ² =0.9 SD=1 p=0.36
Absent	30/52 (57.7%)	32/48 (66.7%)	
Psychiatric comorbidity			
Present	21/52 (40.4%)	12/48 (25%)	X ² =3.3 SD=1 p=0.07
Absent	31/52 (59.6%)	36/48 (75%)	
Age of disorder onset	32.7±10.8	34.7±14	Mann-Whitney U=1193.0 p=0.70
Total number of episodes	2.4±1.7	2.9±2	Mann-Whitney U=1088.0 p=0.25
Duration of current disorder	10.2±12.3	8.1±14.4	Mann-Whitney U=1215.0 p=0.82
Total number of hospitalizations	1.4±0.8	1.8±1.1	Mann-Whitney U=960.5 p=0.02
MMSE score	26.8±2.8	27.6±3.7	Mann-Whitney U=60.0 p=0.53
HDS score	26.9±6	26.3±6.8	Mann-Whitney U=1227.5 p=0.89

ECT: Electroconvulsive therapy; HDS: Hamilton Depression Scale

the other hand, in the ECT treatment group, the first-week treatment response could predict the third-week treatment response with 66.7% sensitivity, 80% specificity, an 88% positive predictive value, and a 52.2% negative predictive value. The results are presented in Table 4.

According to the ROC analysis conducted after the validity analysis, it was shown that a 25% cutoff point in the ECT group and 21% in the antidepressant group had the highest sensitivity and specificity. After determining the cutoff point as 25% for the decrease in HDS scores at the first week in the ECT treatment group, a 60.61% sensitivity, 86.67% specificity, 90.9% positive predictive value, 50% negative predictive value and 4.55% probability were determined. A 25% cutoff point with the antidepressant

group, a 58.62% sensitivity, 76.19% specificity, 77.3% positive predictive value, 57.1% negative predictive value, and 2.46% probability were determined.

DISCUSSION

Treatment response prediction of antidepressant and ECT treatments

The predictability of response at the first week on the response at the third week with antidepressant and ECT treatments in the hospitalized patients who were diagnosed with major depressive disorder was retrospectively investigated in this study.

Table 2. Comparison of socio-demographic and clinical characteristics of subgroups of the ECT group, which were divided into subgroups with respect to a 25% decrease in HDS scores compared to baseline

	Early response present	Early response absent	p
Gender			
Female	19/34 (55.9%)	15/34 (44.1%)	$\chi^2=0.7$ SD=1 p=0.41
Male	6/14 (42.9%)	8/14 (57.1%)	
Working status			
Working	8/19 (42.1%)	11/23 (57.9%)	$\chi^2=1.3$ SD=1 p=0.263
Not working	17/29 (58.6%)	12/29 (41.4%)	
Marital status			
Single	6/14 (42.9%)	8/14 (57.1%)	$\chi^2=1.9$ SD=3 p=0.60
Married	12/22 (54.5%)	10/22 (45%)	
Divorced	2/5 (40.0%)	3/5 (60.0%)	
Widow	5/7 (71.4%)	2/7 (28.6%)	
Psychotic features			
Present	6/11 (54.5%)	5/11 (45.5%)	$\chi^2=0.04$ SD=1 p=0.85
Absent	19/37 (51.4%)	18/37 (48.6%)	
Family history			
Present	13/20 (65.0%)	7/20 (35.0%)	$\chi^2=2.3$ SD=1 p=0.13
Absent	12/28 (42.9%)	16/28 (57.1%)	
Suicide attempts			
Present	13/21 (61.9%)	8/21 (38.1%)	$\chi^2=1.4$ SD=1 p=0.23
Absent	12/27 (44.4%)	15/27 (55.6%)	
Medical disorders			
Present	8/16 (50.0%)	8/16 (50.0%)	$\chi^2=0.04$ SD=1 p=0.84
Absent	17/32 (53.1%)	15/32 (46.9%)	
Age (year)	42.64±15.11	41.13±12	Mann-Whitney U=268.5 p=0.70
Year of education	10.28±5.48	12.17±2.8	Mann-Whitney U=251.5 p=0.45
Total number of episodes	2.56±2.16	3.22±1.9	Mann-Whitney U=208.0 p=0.09
Age of disorder onset	36.80±15.97	32.48±11.33	Mann-Whitney U=250.5 p=0.45
Duration of current disorder	4.60±4	12.04±19.9	Mann-Whitney U=195.0 p=0.05
Number of suicide attempts	1.32±2.04	1.26±2.2	Mann-Whitney U=252.5 p=0.42
Total number of hospitalizations	1.56±1.08	2.13±1	Mann-Whitney U=181.5 p=0.02
MMSE score	27.00±4.47	28.33±2.8	Mann-Whitney U=19.0 p=0.77EKT:

ECT: Electroconvulsive therapy; HDS: Hamilton Depression Scale; MMSE: Mini Mental State Examination.

In total, 68% of patients undergoing ECT and 55.8% of patients undergoing antidepressant treatment reached the response of a 50% decrease in HDS scores compared to baseline. This response to antidepressant treatment is in congruence with the STAR*D study, which reported a 48.6% response rate at the end of 5.5 weeks (22). However, as for the ECT group, the response rate that we detected was lower than the response rates in the literature. In the study of Husain et al. (17), the response rate was indicated to be 79%. The reason might be that hospitalized patients are the ones who remain unresponsive to treatment in outpatient clinics and who are resistant to treatment.

In total, 55.8% of the patients undergoing antidepressant treatment were responsive to treatment by the end of the third week. 62.1% of these patients also showed a 25% decrease in HDS scores at the first week, and at the early stages responded partially to treatment (sensitivity). 78.8% of patients who responded partially at the early stages also responded at the

third week (positive predictive value). It was indicated that the positive and negative predictive values might be more important than sensitivity and specificity during the clinical decision process (12). According to this, an early response predicts the late response through a high positive predictive value (PPV).

The ratio of the unresponsive patients to the antidepressant treatment patients at the first week to the unresponsive patients at the third week was determined to be 62.1% (negative predictive value). The ratio of the unresponsive to the treatment patients at the first week among the patients unresponsive to treatment was 78.3% (specificity). Specificity together with the negative predictive value indicates the predictability of early unresponsiveness to late unresponsiveness. Accordingly, no decrement in HDS scores at the first week by 25% compared to baseline predicts that there will be no decrease in HDS scores at the third week by 50% compared to baseline, as predicted by the 78.3% specificity and 62.1% negative predictive value. In the meta-analysis study of Szegedi et

Table 3. Comparison of socio-demographic and clinical characteristics of subgroups of the antidepressant group, which were divided with respect to a 50% decrease in HDS scores compared to baseline

	Early response present	Early response absent	p
Gender			
Female	17/34 (50.0%)	17/34 (50.0%)	$\chi^2=0.6$ SD=1 p=0.44
Male	7/18 (38.9%)	11/18 (61.1%)	
Working status			
Working	9/27 (33.3%)	18/27 (66.7%)	$\chi^2=3.7$ SD=1 p=0.06
Not working	15/25 (60.0%)	10/25 (40.0%)	
Marital status			
Single	8/11 (72.7%)	3/11 (27.3%)	Fisher's Absolute χ^2 , p=0.68
Married	14/36 (38.9%)	22/36 (61.1%)	
Divorced	2/4 (50.0%)	2/4 (50.0%)	
Widow	-	1/1 (100%)	
Psychotic features			
Present	2/5 (40.0%)	3/5 (60.0%)	Fisher's Absolute χ^2 , p=0.58
Absent	22/47 (46.8%)	25/47 (53.2%)	
Family history			
Present	8/18 (44.4%)	10/18 (55.6%)	$\chi^2=0.83$ SD=1 p=0.86
Absent	16/34 (47.1%)	18/34 (52.9%)	
Suicide attempts			
Present	12/25 (48.0%)	13/25 (52.0%)	$\chi^2=0.07$ SD=1 p=0.80
Absent	12/27 (44.4%)	15/27 (55.6%)	
Medical disorders			
Present	10/22 (45.5%)	12/22 (54.5%)	$\chi^2=0.01$ SD=1 p=0.93
Absent	14/30 (46.7%)	16/30 (53.3%)	
Age (year)	41.42±14.3	40.14±10.9	Mann-Whitney U=319.5 p=0.76
Years of education	10.46±3.7	10.75±3.2	Mann-Whitney U=309.0 p=0.60
Total number of episodes	1.96±1.2	2.82±2	Mann-Whitney U=239.5 p=0.07
Age of disorder onset	35.13±12.5	30.71±8.8	Mann-Whitney U=289.0 p=0.39
Duration of current disorder	6.31±7.4	13.45±14.6	Mann-Whitney U=269.0 p=0.22
Number of suicide attempts	0.79±0.9	0.86±1.8	Mann-Whitney U=327.5 p=0.86
Total number of hospitalizations	1.13±0.3	1.71±1.1	Mann-Whitney U=226.5 p=0.01
MMSE score	27.50±2.7	26.00±3.1	Mann-Whitney U=10.5 p=0.40
MMSE: Mini Mental State Examination.			

Table 4. The predictive value of a 25% decrease in HDS scores at the first week on a 50% decrease in HDS scores at the third week

	PPV	NPV	Sensitivity	Specificity
ECT	22/25 88%	12/23 52.2%	22/33 66.7%	12/15 80%
Antidepressant treatment	18/23 78.3%	18/29 62.1%	18/29 62.1%	18/23 78.3%
ECT: Electroconvulsive therapy; HDS: Hamilton Depression Scale; NPV: negative predictive value; PPV: positive predictive value.				

al. (12) for the predictability of the second-week response on the fourth-week response by SSRIs, 88% sensitivity, 50% specificity, a 50% positive predictive value, and an 86% negative predictive value were determined. In this meta-analysis, the higher negative predictive value than the positive predictive value shows the better prediction of early unresponsiveness on late responsiveness and early responsiveness on late responsiveness. On the other hand, a lower specificity and positive predictive value than sensitivity and negative predictive value indicate that the number of false positives, i.e., the early responsive patients who cannot sustain that response

on late stages, are high. In contrast, our study indicated that the sensitivity and negative predictive value were lower than the specificity and positive predictive value. Therefore, this means that the false negatives, i.e., the unresponsive patients at the first week, but who are responsive at the third week, are much more. This result may arise from an evaluation of the early response at the first week instead of at the second week, distinctly from other studies. If the evaluation was made at the second week, it might be considered that there would be a higher number of patient who had a 25% decrease in HDS scores and a lower number of false negatives.

Lin et al. (14) conducted an ROC analysis in their study, which investigated the prediction of early response with antidepressants on later response, and found that the first-week decrease in HDS scores by 25% predicted responsiveness in 78% of patients (sensitivity), while patients who did not show a 25% decrease at the first week were 61% unresponsive at the end of treatment (specificity). As in our study, a 25% cutoff point enabled the highest sensitivity and specificity values.

There are methodological differences between our approach and Quitkin et al.'s (22) approach, which is the group that enabled the late response hypothesis to become more widespread. Quitkin et al. (23) used "very much improved" and "much improved" ratings for assessing treatment response and moreover they used tricyclic antidepressants and monoamine oxidase inhibitors, which are initially administered at sub-therapeutic doses and that take approximately two weeks to reach therapeutic dose. Thus, the lack of early response observed with antidepressants by Quitkin et al. (23) may be related with the definition of recovery and also with the antidepressants used that were sub-therapeutic in the first two weeks. In our study, we also did not observe an early response in three patients using tricyclic antidepressants. This situation may be explained by administration of this group of antidepressants at low doses in the beginning and then going up to therapeutic doses.

One factor that affects the initial antidepressant response may be the duration of treatment. For instance, in Watanebe et al.'s (24) meta-analysis, in which they compared the effectiveness of mirtazapine in terms of efficiency and the onset of efficiency with other antidepressants, it was reported that there were no differences in the efficiency of six weeks and ten weeks treatment but the effect of mirtazapine started faster in the early period (24). Although the number of patients who used mirtazapine was quite low ($n=3$), it is interesting that all of these patients responded to treatment earlier. Fast dose titration is also a factor related with early recovery. For example, Bernardo et al. (25) reported that with venlafaxine, faster dose titration provides a faster improvement in the depressive symptoms compared to slow dose titration. Frequently used fast dose titrations in inpatients at our clinic may be a factor increasing the early response rates.

With the administration of ECT, 52% of the patients showed a 25% decrease from the initial HDS score at the first week and after approximately 3 ECT administrations. This finding is similar to Husain et al.'s (17) study that reported a response rate of 53.8%. At the third week, 88% of these patients showed a 50% decrease in HDS scores (positive predictive value). Of all the patients who responded to treatment at the third week, 66.7% also responded to treatment partially at the first week (specificity). Of the patients that did not show a 25% decrement in HDS scores at the first week, 52.2% were unresponsive also at the third week (negative predictive value). Eighty percent of patients who did not respond to treatment at the third week were found not to respond to treatment also in the first week (specificity). These findings demonstrate that the early response to ECT predicts a late response through a high PPV. Early unresponsiveness is also a predictive factor for late unresponsiveness with high specificity. The sensitivity and NPV being lower than specificity and PPV also indicates that the number of false negatives, meaning patients giving late response to treatment, was higher. This situation, as previously stated, may be rooted in the early assessment of the early response at the first week.

There is no study in the literature that focuses on the investigation of predictability of early response to ECT on the ultimate response. However, Husain et al., in their study where they investigated the speed of early response to ECT, tried to determine an early response cutoff point by using ROC analysis to predict the ultimate response, but they could not find a clinically significant threshold value at the fifth ECT. When they investigated the predictability of a 30% decrease in HDS scores at the sixth ECT,

they found that 61% of the patients who did show a 30% improvement responded to ECT at the end of treatment, and also that responding to ECT by a 30% improvement was a clinically significant indicator to continue with ECT. However, they concluded that the lack of a 30% improvement could not be predictive of ultimate unresponsiveness.

The effect of socio-demographic and clinical characteristics on the response to treatment in the antidepressant medication and ECT groups

When the ECT and antidepressant groups were compared with respect to socio-demographic and clinical characteristics, only the number of hospitalizations in the ECT group was determined to be higher; but no other differences with respect to the other characteristics that point to a more severe disorder in the ECT group were found.

The antidepressant and ECT groups were assigned to subgroups based on their previously established response to treatment criteria according to their responsiveness or unresponsiveness to treatment and they were compared with respect to their clinical and socio-demographic characteristics. It was found that in the ECT group, none of the factors of age, gender, marital status, years of education, previous suicide attempts, psychotic features, family history, and MMT score at admission had an impact on the response observed at the first week, and also it was determined that for the inpatients who did not respond to treatment, the number of total hospitalizations and the duration of the current episode were significantly higher. Similar findings were obtained in the antidepressant group when factors acting upon the response to treatment at the first week were taken into account. While in the antidepressant group, the number of hospitalizations was significantly higher in the subgroup who did not respond to treatment at the first week, no other statistical significance was determined with respect to the socio-demographic and clinical characteristics. The factors that impact on the treatment response observed at the third week were the presence of medical illness in the ECT group, length of the current episode duration, the duration of the disorder, higher number of previous hospitalizations, and total number of episodes. These factors pointing toward the chronicity of the disorder were found to be related with unresponsiveness. As for the antidepressant group, psychiatric comorbidity was found to be related with unresponsiveness to treatment.

In a study investigating the factors that predict treatment response in inpatients, the presence of suicide attempts, severity of the disorder at the onset, a duration of the episode of less than 24 months, a lower number of hospitalizations, and the absence of psychiatric comorbidity were reported to predict treatment response (26). Similarly, Seemüller et al. (27) found in their study, where the treatment response of 1014 inpatients and factors that influence the response were investigated, that the duration of the current episode, the presence of comorbidity, and a history of previous hospitalizations were negatively related with the treatment response, while the severity of the disorder and suicidality were found to be positively related. In the present study, it was seen that the presence of comorbidity and the total number of hospitalizations were related with unresponsiveness to antidepressant treatment, which is compatible with the literature.

There are not enough studies in the literature investigating the factors that contribute to the response to ECT treatment. In a study involving patients under the age of 65, the presence of psychotic depression, being unresponsive to antidepressant medication, and the presence of a personality disorder were determined to be factors related with unresponsiveness to treatment (28). There is no one-to-one correlation between the results of this study and our study. In our study, the determined unresponsiveness to ECT treatment was considered to be related with chronicity of the disorder.

One of the limitations of the present study is the insufficiency of the duration of follow-up, which is rooted to the retrospective nature of the study. Accordingly, instead of four or six weeks follow-up, which is common in literature, the status of the patients after three weeks of treatment were assessed. Another limitation is that the response to ECT treatment, which has a fast effectiveness, was assessed with weekly administered depression scores, and thus, immediate improvement after ECT may have been overlooked. Moreover, the lack of evaluation with respect to depression subtypes is another limitation to mention.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University School of Medicine.

Informed Consent: Informed consent was not taken from the patients, due to data were obtained from patient files retrospectively.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.U., A.Ç., Z.T., A.T.; Design – H.U., A.Ç., Z.T., A.T.; Data Collection and/or Processing – A.Ç.; Analysis and/or Interpretation – H.U., A.Ç., Z.T., A.T.; Literature Search – H.U., A.Ç., A.T.; Writing Manuscript – A.Ç., H.U.; Critical Review – H.U., A.Ç., A.T., Z.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

- Lepine JP, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat* 2011; 7(Suppl 1):3-7.
- Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, Whiteford HA. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol Med* 2013; 43:471-481. [CrossRef]
- Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013; 10:e1001547. [CrossRef]
- Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv* 2009; 60:1439-1445. [CrossRef]
- Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, Parikh SV, Patten B, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord* 2009; 117(Suppl 1):26-43. [CrossRef]
- Crison ML, Trivedi M, Pigott TA, Rush AJ, Hirschfeld RM, Kahn DA, DeBattista C, Nelson JC, Nierenberg AA, Sackeim HA, Thase ME. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. *J Clin Psychiatry* 1999; 60:142-156. [CrossRef]
- American Psychiatric Association. Practice Guideline for the Treatment of the Patients with Major Depressive Disorder. Available from: <http://psychiatryonline.org/guidelines>, Erişim tarihi: 17.12.2014.
- Nierenberg AA, Faraburgh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF, Fava M. Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry* 2000; 157:1423-1428. [CrossRef]
- Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry* 2006; 63:1217-1223. [CrossRef]
- Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. *Eur Neuropsychopharmacol* 1993; 3:127-135. [CrossRef]
- Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. *Neuropsychopharmacology* 2004; 29:566-579. [CrossRef]
- Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry* 2009; 70:344-353. [CrossRef]
- Li J, Kuk AYC, Rush AJ. A practical approach to the early identification of antidepressant medication non-responders. *Psychol Med* 2011; 43:309-316.
- Lin C, Lane HY, Chen CC, Juo SH, Yen CF. Early prediction of fluoxetine response for Han Chinese inpatients with major depressive disorder. *J Clin Psychopharmacol* 2011; 31:187-193. [CrossRef]
- Bozkurt A. Depresyonda diğer biyolojik sağaltımlar Elektro Konvülfiz Terapi. Yazıcı O, Oral ET, Vahip S, editörler: Depresyon Sağaltım Kılavuzu Kaynak Kitabı içinde. Türkiye Psikiyatri Derneği Yayınları; 2008. s. 119-129.
- Rodger CF, Scott AIF, Whalley LJ. Is there a delay in the onset of the antidepressant effect of electroconvulsive therapy? *Br J Psychiatry* 1994; 164:106-109. [CrossRef]
- Husain MM, Rush AJ, Fink M, Knapp R, Rummans T, O'Connor K, Rasmussen K, Little M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, Kellner CH. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a consortium for research in ECT (CORE) report. *J Clin Psychiatry* 2004; 65:485-491. [CrossRef]
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62. [CrossRef]
- Akdemir A, Örsel SD, Dağ İ. Hamilton Depresyon Derecelendirme Ölçeğinin geçerliliği-güvenilirliği ve klinikte kullanımı. *3P Dergisi* 1996; 4:251-259.
- Folstein MF, Folstein M, Hugh PR. Mini Mental State A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198. [CrossRef]
- Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Standardize Mini Mental Test'in Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. *Türk Psikiyatri Dergisi* 2002; 13:273-281.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; 163:1905-1917. [CrossRef]
- Quitkin FM, McGrath PJ, Stewart JW, Taylor BP, Klein DF. Can the effects of antidepressants be observed in the first two weeks of treatment? *Neuropsychopharmacology* 1993; 15:390-394. [CrossRef]
- Watanabe N, Omori IM, Nakagawa A, Cipriani A, McGuire H, Churchill R, Furukawa TA. Multiple Meta-Analysis of New Generation Antidepressants (MANGA) Study Group. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. *J Clin Psychiatry* 2008; 69:1404-1415. [CrossRef]
- Bernardo M, Busian E, Duran A, Soler-Insa PA, Alberni J, Prieto R. Venlafaxine titration dosage in depressive inpatients: a series of cases. *Actas Esp Psiquiatr* 2003; 31:31-34.
- Riedel M, Möller HJ, Obermeier M, Adli M, Bauer M, Kronmüller K, Brieger P, Laux G, Bender W, Heuser I, Gaebel W, Schennach-Wolff R, Henkel V, Seemüller F. Clinical predictors of response and remission in inpatients with depressive syndromes. *J Affect Disord* 2011; 133:137-149. [CrossRef]
- Seemüller F, Riedel M, Obermeier M, Bauer M, Adli M, Kronmüller K, Holsboer F, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Dichgans E, Böttländer R, Musil R, Möller HJ. Outcomes of 1014 naturalistically treated inpatients with major depressive episode. *Eur Neuropsychopharmacol* 2010; 20:346-355. [CrossRef]
- Vreede IM, Burger H, Vliet IM. Prediction of response to ECT with routinely collected data in major depression. *J Affect Disord* 2005; 86:323-327. [CrossRef]