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Original Article

Remission Rates, Time to Remission, and Related Factors in Adolescents with Major Depressive Disorder

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ABSTRACT

Objective: Major depressive disorder (MDD) is a common disorder in children and adolescents that can cause serious morbidity and mortality. Although response rates to treatment are high, less than half of the adolescents with MDD achieve remission. The present study aims to evaluate remission rates, time to remission, and the predictors of remission in adolescents with MDD.

Methods: This study included 34 adolescents with MDD who were followed-up for a minimum period of 120 days. The adolescents were assessed with the Clinic Global Impression Scale, Beck Depression Inventory, Young Mania Rating Scale, Child Mania Rating Scale, and Screen for Child Anxiety-Related Emotional Disorders at the baseline and at weeks 4, 8, and 12.

Results: 67.6% of the adolescents had at least one comorbid diagnosis. The remission rate at week 12 was 73.5%. The mean time to remission was 72.0 days. The female adolescents achieved a significantly higher remission rate than the males.

Conclusion: The majority of adolescents achieved remission following acute treatment, and that the time to remission for the female adolescents was shorter compared with the males. Remission time does seem neither to be related to the number of medications prescribed nor to the number of comorbid diagnoses.

Keywords: Adolescent depression, treatment outcomes, remission

INTRODUCTION

Major depressive disorder (MDD) with a prevalence of 4-8% is one of the most common mental disorders in children and adolescents.[1,2] Although recovery is usually observed following the first episode of depression that occurs during adolescence, follow-up studies have reported an 80% recurrence rate.[3] The treatment of depression consists of three phases: the acute phase, the continuation phase, and the maintenance phase. The aim of the acute phase is to achieve a rapid improvement in the symptoms, while the continuation phase aims to achieve a sustainable and permanent remission of symptoms. Finally, prevention of a recurrence is the primary objective of the maintenance phase. While the acute and continuation phases are relevant to all patients in the treatment of depression, it is recommended that the maintenance phase only be implemented to selected children exhibiting risk factors to prevent the occurrence of new episodes.[4] If depression is not properly treated, recurrent episodes may continue during an individual's lifetime, leading to an impairment of academic and social life and an increased risk of suicide.[5]

Although the treatment response, which is defined as a 50% improvement from baseline on the standardized rating scales, is taken into consideration in the evaluation of the treatment

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efficacy, the main goal of treatment is to achieve remission, which is an improvement in the symptoms, so that the individual no longer meets the criteria of a depressive disorder and has minimal symptoms.[6] Relapse and recurrence rates increase in patients who respond to treatment but who do not achieve remission. However, the patients who have been successfully treated and who have achieved complete remission will not face such a high risk if their treatment is properly managed.[3] Therefore, achieving remission is crucial for the long-term treatment of depression by reducing the risk of relapse, suicide, and substance abuse, increasing the quality of life and avoiding increased healthcare costs caused by depression.[7]

Short- and long-term changes in symptoms with pharmacotherapy and/or psychotherapy in adolescents diagnosed with MDD have been drawing increased attention recently; however, the data are mostly obtained from naturalistic follow-up studies. Although "response" alone remains insufficient to assess the outcome of treatment, and "remission" has been reported as the gold standard for the efficacy of treatment,[8] the most common criterion to determine the effectiveness applied in clinical studies conducted to date has been "response." In this study, the aim was to determine remission rates, the duration of remission, and predictors of remission obtained as a consequence of acute treatment in adolescents with MDD.

METHODS

This study was designed as a naturalistic and retrospective study. The study protocol was approved by the Ethics Committee of AIBU (Abant Izzet Baysal University) (protocol/serial number: 2018/163). Participants' parents provided a written informed consent before the scales were applied.

Sample

The sample of the study consisted of adolescents between the ages of 12 and 17 who were admitted to the Department of Child and Adolescent Psychiatry at Abant Izzet Baysal University (AIBU) School of Medicine, diagnosed with MDD and treated between 2011 and 2013.

Main Points

- The importance of irritability in adolescent depression may increase the use of atypical antipsychotics in pharmacological treatment.
- Remission rates of adolescents were reported to be between 23 and 63% after 12 weeks of treatment. In this study, the remission rate at week 12 was found to be 73.5%. The ambiguous definition of the concept of remission and different measurement methods that can be used to measure remission may affect the wide range of remission rates.
- There are several factors related to the achievement of remission such as the age of onset, gender, level of functioning, duration of depressive episode, and comorbidities. In the current study, no significant difference was identified in relation to the times in achieving remission according to the number of comorbidities; however, it was found that female adolescents achieved remission in a shorter time and at a higher rate than males.

The inclusion criteria were as follows:

(a) 12-17 years of age;
(b) Meeting the advanced Diagnostic and Statistical Manual of Mental Disorders criteria for MDD;
(c) Existence of follow-up data for at least 120 days;
(d) No missing data in the outpatient clinic records; and
(e) Absence of bipolar disorder, psychotic spectrum disorder, mental retardation, autistic spectrum disorder, substance use disorder, and any neurological disorders.

In addition, it was required that the assessments at the baseline and at weeks 4, 8, and 12 include a Clinic Global Impression Score (CGI), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS), Child Mania Rating Scale (CMRS), and a Screen for Child Anxiety Related Emotional Disorders (SCARED). At the last visit, adolescents with a CGI score of 1 or 2 were considered to be in remission.[9]

The number of patients admitted with depressive complaints between the dates is 3,034. Three hundred and twenty-eight of them are considered to meet the diagnosis of MDD according to diagnostic and statistical manual of mental disorders-IV (DSM IV) criteria, and 34 of the MDD patients who met the inclusion criteria mentioned above were included in the study. Among the cases that met the diagnosis of MDD, the most case loss occurred due to the incomplete 120-day follow-up period ($n = 165$) and missing data in the file ($n = 59$).

Assessment Scales

- *BDI*: The BDI is a 21-item multiple choice self-reporting inventory consisting of symptoms and attitudes related to depression. The items have a total summed score range of 0-63, with the higher numbers indicating an increase in the severity of depression. The standard cutoff scores are as follows: 0-9, indicating minimal depression; 10-18, indicating mild depression; 19-29, indicating moderate depression; and 30-63, indicating severe depression. A validity and reliability study in Turkish was performed by Hisli for this scale.[10]
- *SCARED*: The SCARED was developed as a screening tool for both children and their parents that would encompass several categorizations of anxiety disorders: somatic/panic, generalized anxiety, separation anxiety, social phobia, and school phobia. It is accepted that a total score of $\geq$25 may indicate the presence of anxiety disorder.[11] A validity and reliability study in Turkish for this scale was conducted by Çakmakcı.[12]
- *YMRS*: The YMRS is an 11-item tool, which is applied by a clinician. The items on the scale rank symptoms of mania by five clearly defined grades of severity. The YMRS yields a score ranging from 0 to 60, with higher scores representing a more severe psychopathology. It is accepted that a total score of $<$12 indicates euthymia. A Turkish validity and reliability study in Turkish was conducted for this scale by Karadağ et al.[13]
- *CMRS*: CMRS is a 21-item diagnostic screening tool developed by Pavuluri et al.[14] designed to identify the symptoms of mania in children and adolescents aged

Table 1. Comparing Baseline Scales Score of Adolescents

	Male	Female	Total	z	*P*	r
Number of comorbidity	1.7 (1.0)	1.8 (1.3)	1.7 (1.1)	–0.1	.9	–0.017
Baseline CMRS score	7.8 (5.3)	19.8 (13.0)	10.6 (9.0)	–2.5	.01	–0.43
Baseline YMRS	6.5 (5.1)	5.0 (0.0)	6.1 (4.4)	–0.3	.9	–0.293
Baseline BDI	21.9 (7.7)	28.1 (11.1)	24.4 (9.6)	–1.7	.1	–0.189
Baseline SCARED	35.0 (17.0)	41.8 (14.5)	37.7 (16.1)	–1.2	.3	–0.293
Baseline CGI	4.4 (0.7)	4.7 (0.9)	4.5 (0.8)	–1.1	.3	–0.172

Abbreviation: CMRS, Child Mania Rating Scale; YMRS, Young Mania Rating Scale; BDI, Beck Depression Inventory; SCARED, Screen for Child Anxiety and Related Disorders; CGI, Clinic Global Impression Scale.

between 9 and 17. Although a validity and reliability study in Turkish has not been conducted for this scale, it is used for screening mania symptoms by clinicians in Turkey.

- *CGI-Improvement Scale (CGI-I)*. CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened in comparison to the baseline.[15] CGI-1 indicates very much improvement-nearly all better and good level of functioning, and CGI-2 indicates much improvement—notably better with significant reduction of symptoms. In this study, adolescents with a CGI score of 1 or 2 were considered to be in remission.[9]

Data Analysis

The data obtained by the study were evaluated using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc.; Chicago, IL, USA). Some of the sociodemographic and clinical categorical variables of the cases were assessed based on numbers and percentage values. A Chi-square test was used to compare the categorical variables. Remission time was recorded on a daily basis and evaluated based on a Kaplan–Meier survival analysis. *P*-values $<.05$ were considered significant.

RESULTS

Thirty-four adolescents were included in the study during the study period. The mean age of the adolescents was 15.3 $\pm$ 0.9. The number of male patients was 20 (58.8%) and female patients was 14 (41.2%). The comparison of the baseline scale scores according to gender is given in Table 1. Nonparametric tests were used in comparisons where the data were not normally distributed (Man–Whitney U Test). When the number of comorbidities, and BDI, CMRS, and CGI scores were compared by gender, significant differences were observed between the CMRS scores ($P = .001$), whereas no significant difference was seen between the other values ($P > .05$).

67.6% of the cases had at least one comorbidity. The most common comorbid diagnosis was anxiety disorder (67.6%). Fifty percent of the cases had a psychopathology in the family history, and it was learnt that 61.8% had presented to other clinics for depressive complaints in the past. 91.2% of the patients were started on medication after the initial evaluation. The most commonly used drugs were atypical antipsychotics (AAP) (79.4%) and selective serotonin reuptake inhibitors (SSRIs, 55.9%). The remission rate was 73.5% (n = 25) at week 12 of the treatment. Female adolescents had significantly higher remission rates than males (Chi-square = 6.8, $P = .01$, $\pi = 0.5$). A posthoc power analysis based on Chi-square results achieved 0.60 power. The mean time to remission in our sample was 72.0 (SD 22.9) days (mean: 55.7 $\pm$ 20.7 days for females and 78.3 $\pm$ 20.9 days for males, Mann-Whitney U test, Z = –2.4, $P = .03$). A posthoc power analysis based on Mann–Whitney U test results achieved 0.99 power. Comparison of remission time in girls and boys according to comorbidities was done with Kaplan–Meier survival analysis (Figures 1 and 2). The Kaplan–Meier test revealed that the remission time did not differ based on the number of comorbidities.

DISCUSSION

In this study, which examined time to remission and factors related to remission in the acute treatment in adolescents with MDD, the most frequently prescribed drug for depressive adolescents was found to be AAP. Although the clinical appearance of depression in children and adolescents is similar to adult depression in terms of core symptoms, it also displays some important differences. Instead of expressing depressive feelings, children and adolescents may exhibit emotional volatility, irritability, low frustration tolerance, anger outbursts, and related destructive behavior.[16,17] While cognitive behavioral therapy is recommended as the first-line treatment for mild to moderate MDD in children and adolescents, SSRI are recommended as the first-line treatment in moderate to severe MDD cases.[18] AAPs are used for adjuvant treatment in resistant depression and are prescribed as an additional treatment to an antidepressant.[1] Although SSRIs are recommended as the first choice in the pharmacological treatment of MDD, it was thought that prescription of AAPs rather than SSRIs in the present study may be due to the fact that irritability is at the forefront in the clinical appearance of adolescent depression or that parents put higher emphasis on irritability, especially in

Figure 1. Time to remission according to number of comorbidities in males.

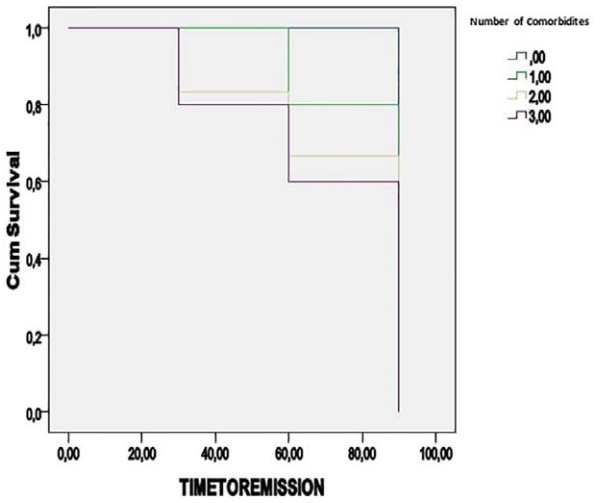
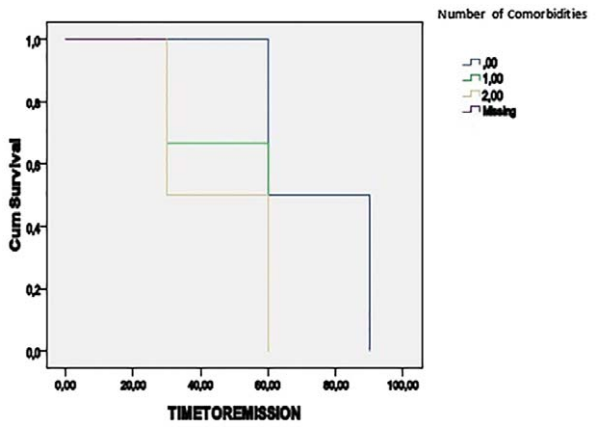


Figure 2. Time to remission according to number of comorbidities in girls.



girls, and there is an expectation that it should resolve as soon as possible. In support of this proposition, female adolescents did not show a significant difference in the YMRS as evaluated by a clinician, while they received significantly high scores from the CMRS completed by their parents.

Remission rates of adolescents were reported to be between 23 and 63% after 12 weeks of treatment.[19] The treatment for adolescents with depression study (TADS) reported that the remission rate to be 23% in adolescents after 12 weeks of acute treatment. However, at week 36, remission rates were increased to 60%, demonstrating the importance of maintenance therapy.[20] In the current study, the remission rate at week 12 was found to be 73.5%. One of the issues most widely discussed in the literature is the ambiguous definition of the concept of remission. Different measurement methods can be used to measure remission, which is defined as a state of minimal to no symptoms with restoration of normal functioning. Remission measurements in clinical trials are commonly based on the cutoff scores from standardized scales. For example, a Hamilton Depression Score of seven or less, a Montgomery-Asberg Depression Scale score of 10 or less, or a Clinical Global Impression (CGI) score of one or two is typically defined as remission. Some studies in the literature relating to child and adolescent psychiatry have used a child depression rating scale score of 28 or lower to define remission.[20–24] The remission rates obtained in the present study may be high as we adopted a more flexible definition of remission (CGI 1 or 2) as suggested by the American College of Psychopharmacology.[25] In addition, we think that the long time allocated to a patient (45 minutes for each interview) in our polyclinic, which is also an education clinic, contributes to the high remission rates by strengthening the therapeutic relationship.

In general, factors related to the reduction in symptoms and the achievement of remission are the age of onset, gender, level of functioning, duration of depressive episode, number of comorbidities, existing melancholic features, suicidal ideation and feelings of hopelessness, and the patient's expectations from the treatment.[26–28] In this study, no significant difference was identified in relation to the times in achieving remission according to the number of comorbidities; however, it was found that female adolescents achieved remission in a shorter time and at a higher rate than males. A recent study that investigated the course of the acute phase symptoms of depressed teens enrolled in TADS indicated that a group consisting of adolescents with severe depression achieved early improvement with treatment (high severity-early improvement group). Most of the patients in the high severity-early improvement group in the said study were female.[5] In line with this finding, it was observed, although at a level of significance, that female depressive adolescents had higher depression scores than the males at the beginning of treatment; however, they achieved remission in a shorter time compared with the males.

The current study had several limitations. The results obtained in this study may not be generalized as it was a single-center study conducted on a selected clinical sample. The small sample size and the fact that the scales used are based on self-reporting are amongst those limitations. The short follow-up period can also be considered as a limitation. The remission achieved at week 12 may be a spontaneous remission, or a short-term remission that will be followed by a relapse during a longitudinal follow-up.

The data obtained in this study consist of naturalistic and retrospective data. It is recognized that a placebo response is higher in such studies. The findings need to be supported by multicentered longitudinal studies with a larger sample size.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Abant İzzet Baysal University (AIBU) (protocol/serial number: 2018/163).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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