

Psychoeducation Can Ameliorate Somatic and Manic Symptomatology in Youth at High-Risk for Bipolar Disorder: A Randomized-Controlled Study

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Abstract

Background: Given the high hereditary rates for bipolar disorder (BD), offspring of BD patients (high-risk [HR] group) are perfect candidates for research on early detection and prevention strategies. Psychoeducation is a structured and systematic intervention, in which the knowledge of the illness and its treatment is transferred to the patient and/or family in a didactic approach and it is a core component of psychotherapeutic interventions. Several studies which explored the effectiveness of these interventions in HR youth reported positive out-comes; but these were mainly focused on symptomatic HR and none of them were done among asymptomatic HR. Therefore with this study, we aimed to evaluate the effect of psychoeducational intervention on asymptomatic HR youth.

Methods: In this prospective randomized controlled study, total of 60 cases (aged between 11 - 18 years) were enrolled and randomized into two group as cases who received psychoeducational intervention (PE+) (n=30) and who did not receive psychoeducational intervention (PE-) (n=30) on the first visit (T0). Groups were evaluated regarding their psychiatric symptomatology and quality of life (QoL) using DSM-5 Level 1 Cross-cutting Symptom Scale Child Form (CCSS-5) and Pediatric Quality of Life Questionnaire throughout four interviews with 3-month intervals (T0 - T3). Total of 14 cases in PE+ and 10 cases in PE - group were diagnosed with at least one psychiatric disorder in the duration of the study and one case in PE+ dropped-out from the study without further notice; so total of 15 children in PE+ and 20 children in PE - group completed all of the interviews.

Results: Ages of PE+ group ranged between 10.58 and 17.58 years (mean[±SD]=14.80[±2.56]) and PE - group ranged between 10.83 and 17.25 years (mean[±SD]=13.83[±2.33]). Male participants comprised 66.67% of PE+ group and 56.67% of PE - group. There was no statistically significant difference between groups regarding age (p=0.096) and gender (p=0.426). Even though psychoeducation did not have effect on QoL of the high-risk population; overall reduction in somatic (p<0.001) and manic (p=0.026) symptom severity in CCSS-5 was more distinct for PE+ group compared to PE - group. There were no significant effects of psychoeducation on the other subscales of CCSS-5.

Conclusions: Improvement in affective symptomatology with CBT and longer remission periods with FFT can be explored in the same scope with the overall reduction in manic symptom severity we showed in PE+ group. Overall reduction in somatic symptom severity of PE+ group might be due to the positive effect of psychoeducation on family communication and problem-solving skill. However, there is no previous research indicating the presence of somatic symptoms/somatization disorders among HR youth; so whether somatic symptoms are the consequences of family conflict or a core component of prodromal phase of BD is still unclear. Studies state that psychological interventions are most effective if they are performed in the early stages of BD; therefore asymptomatic HR youth are critical for prevention strategies and more studies are needed in this population.

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INTRODUCTION

Bipolar Disorder (BD) is a chronic, recurrent and potentially severe psychiatric disorder which affects 0.6-2.4% of adult population and roughly 2% of youth under the age of 18 [1,2]. In the literature, BD diagnosis among parents is the

most frequently replicated risk factor for developing BD and children of parents with BD diagnosis have 10-15 fold increased risk for having a BD themselves, thus they are called “high-risk (HR)” or “at-risk” group [3,4]. Despite BD

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is often reported to be initially diagnosed (age of onset) at the age of 18; more than half of adult patients with BD present their first episode before the age of 18 [5,6]. Early recognition of BD is clinically important because delays in diagnosis and treatment have been associated with longer depressive episodes, higher suicidality, shorter euthymic periods and poorer functioning in adulthood [7,8].

For early intervention purposes research focused on early detection of “symptomatic HR” children, which can be defined as HR group who does not meet the criterion for any psychiatric disorder but has psychiatric symptoms with an apparent decrease in global functioning. Studies with prospective designs conducted in symptomatic HR group indicate that; before the first manic episode, BD has a prodromal phase characterized by subthreshold mood symptoms (mood lability, depressive and manic symptoms) and additional unspecific symptoms (sleep disturbances, anxiety and substance use disorders) [3,9,10]. The Course and Outcome of Bipolar Youth (COBY) study reported that 25% of youths with manic symptoms who did not meet the criteria for a diagnosis of manic/mixed episode (i.e. bipolar disorder not otherwise specified, BD-NOS) had converted to BD-I or BD-II at a 2-year follow-up [11]. In addition to BD-NOS; several other studies found that children with major depression diagnosis who also have elevated mood with irritability and rapid mood fluctuations (cyclothymia)/mood lability were more likely to develop a manic episode in the follow-up evaluations [12-14]. Symptomatic HR group seems to be good candidates for determining the efficacy of early intervention modalities for BD. For example; psychosocial interventions might play a protective role by facilitating symptomatic HR children and adolescents with social support, autonomy and stress-coping skills [15,16]. However, there is no evidence on pharmacological treatments for symptomatic HR group or no consensus on which intervention modalities are most effective in preventing symptom progression [16,17].

Psychoeducation can be described as a structured and systematic intervention, in which the knowledge of the illness and its treatment is transferred to the patient and/or family in a didactic approach [18]. It is a rather easy instrument to utilize in a rather short time periods, which is a valuable feature considering the large amount of daily referrals and limited durations of psychiatric appointments seen in daily psychiatric practices in public hospitals. Psychoeducation has found to be effective in the treatment of adolescents with depression, anxiety disorders, attention deficit and hyperactivity disorder and behavioral addictions [19-22]. It is a core component of psychotherapies such as cognitive-behavioral therapy (CBT), family focused therapy (FFT) and interpersonal and social rhythm therapy (IPSRT) [23-25]. Even though there are no research done in asymptomatic HR group; studies on psychotherapeutic interventions which includes psychoeducation in symptomatic HR group have reported positive results. Nadkarni and Fristad (2010) showed that symptomatic HR youth who received multi-family psychoeducational psychotherapy had lower conversion

rates to BD spectrum disorders after a 1-year follow-up [26]. In a study done by Leopold et al. (2020), total of 75 patients with subthreshold bipolar symptoms who also have a positive family history of mood disorders (BD, major depressive disorder or schizoaffective disorder) were randomized to CBT or unstructured group meetings. They found that, although there was no difference between groups, both groups showed improvement in affective symptomatology and global functioning [25]. In another study, Miklowitz et al. (2013) found that; compared to brief family education, symptomatic HR youth who received FFT (which consists of family psychoeducation, communication skills training, and problem-solving skills training) had shorter durations of mood symptoms and longer durations of remission [23]. A recent FFT study in youths with a family history of BD who show early signs of depression or subthreshold mania/hypomania also demonstrated an association between FFT and longer times between mood episodes [16]. In addition, Goldstein et al. (2014) presented positive findings regarding IPSRT in their pilot study conducted on symptomatic HR youths [24].

Both follow-up and intervention studies were done with symptomatic HR group, which means subjects were included when their symptoms are severe enough for them or their families to seek admission for assessment and treatment [27]. So despite their substantial commentaries on the trajectories of prodromal BD, development of the disorder itself and prevention strategies; they say little to none about “asymptomatic HR” children, who has a parent with BD but does not manifest psychiatric symptomatology severe enough to disrupt the global functioning. Even though there are several studies investigating the effects of intervention strategies for BD; none of them were done in asymptomatic HR sample [15,16,23,24,26,28]. In addition, studies in the literature state that psychological interventions are more effective in the early stages of BD compared with the later stages [29]. Therefore with this study, we aimed to evaluate the effect of psychoeducational intervention, which can be easily administered in public hospitals, on the symptomatology and quality of life of asymptomatic HR children and adolescents. We hypothesized that, children who received psychoeducational intervention will have higher quality of life and lower psychiatric symptom scores all throughout the study period compared to children who did not receive psychoeducational intervention.

METHODS

Study Sample

This study was designed as a prospective randomized, controlled study. BD patients whose psychiatric follow-ups were done by the Rize Training and Research Hospital Psychiatry Department of our institution were contacted in order to enroll their HR children to the study. A power analysis could not be done because precedent similar studies were lacking; so recruitment was planned to span across

one year period (between December 2018 and December 2019). Total of 78 children who are between the ages of 11 - 18, whose parents were diagnosed with BD and who did not receive any psychiatric treatment (medication or therapy) prior to the study were initially recruited. All of the children were evaluated via semi-structured psychiatric interviews (Schedule for Affective Disorders and Schizophrenia for School Aged Children Kiddie-SADS-lifetime Version [K-SADS-PL]) by a trained professional (same clinician all throughout the study period) and 18 children who received a psychiatric diagnosis (except for attention deficit and hyperactivity disorder diagnosis) according to K-SADS-PL were excluded from the study. Total of 60 children with BD parents, who did not receive any psychiatric diagnosis according to K-SADS-PL and did not have any history of headache (because headache symptoms might interfere with the somatic symptom subscale of psychiatric symptom scale), head trauma or neurological disease were included and randomized. Simple randomization was done using sealed envelopes (30 including letter A and 30 including letter B). Cases which got letter A comprised the group who received psychoeducational intervention (PE+) and cases which got letter B comprised the group who did not receive psychoeducational intervention (PE-) in the first clinical interview (T_0). Both groups underwent total of 3 follow-up clinical interviews (T_1 , T_2 and T_3) with intervals of 3 months. DSM-5 Level 1 Cross-Cutting Symptom Scale Child Form (CCSS-5) and Pediatric Quality of Life Inventory were used for evaluation in all of the interviews ($T_0 - T_3$). Children who scored higher than thresholds for subscales of CCSS-5 in each interview were further evaluated with K-SADS-PL to determine if they have a psychiatric diagnosis or not during the follow-ups. Cases who received a psychiatric diagnosis according to K-SADS-PL in the follow-up interviews were removed from the study and started on appropriate psychiatric treatment. Participants could be given a psychiatric diagnosis in any of the interviews ($T_0 - T_3$) and total of 14 cases in PE+ and 10 cases in PE - group were diagnosed with a psychiatric disorder in the duration of the study (psychiatric diagnoses were; 11 cases with attention deficit and hyperactivity disorder [45.84%], 6 cases with major depressive disorder [25%], 5 cases with conduct disorder [20.83%] and 2 cases with BD [8.33%]) and there were no comorbidities. In addition one case in PE+ dropped-out from the study without further notice and did not specify a reason; so total of 15 children in PE+ and 20 children in PE - group completed all of the interviews. A CONSORT flow diagram summarizing case recruitment and study process is presented in Figure 1.

This research has been approved by the ethics committee of the institution in which it was conducted (approval date - 14 November 2018; approval number - 158) and was carried out in accordance with the ethical guidelines, including the World Medical Association (1975) Declaration of Helsinki - Ethical Principles For Medical Research Involving Human Subjects revised in 2013. All of the participants and their parents gave their informed consent prior to their inclusion to the study after the procedures had been fully explained.

Measures

Schedule for Affective Disorders and Schizophrenia for School Aged Children Kiddie-SADS-lifetime Version (K-SADS-PL): This semi-structured psychiatric interview was adapted from the original version by Kaufman et al. (1997) in order to use for evaluation and diagnosis of psychiatric disorders in childhood and adolescence [30]. This semi-structured psychiatric interview includes total of 5 diagnostic areas (mood disorders, psychotic disorders, anxiety disorders, conduct disorders, substance abuse/misuse and other disorders) and should be performed on both the parents and the child. It has been found to be valid and reliable in Turkish language [31].

Psychoeducational Interventions for the Parents of High-risk Children and Adolescents: This psychoeducational intervention was adapted from the “Psychoeducational Therapy in Mood Disorders of Children and Adolescents - Parent Version”, which is a book prepared and translated in accordance with the research done by West and Pavuluri (2009) on the psychosocial interventions for children and adolescents with mood disorders [32,33]. Booklet and the interview include definitions and characteristics of manic/hypomanic/ depressive episodes, risk groups for mood disorders, suicide, psychosis and psychosocial arrangements for high-risk children. Translated version of the psychoeducational intervention booklet is provided as a supplementary file with the manuscript.

DSM-5 Level 1 Cross-cutting Symptom Scale Child Form (CCSS-5): CCSS-5 is a self-report scale provided by American Psychiatry Association [34]. It evaluates the psychiatric areas important for the diagnosis of psychiatric disorders and aims to help clinicians identify areas which can be important in the treatment and prognosis. In addition, it can also be used to monitor the changes of the symptomatology among the treatment period. It is utilized for children and adolescents between the ages 11 and 18. It comprises of 25 items which assesses 12 psychiatric domains such as; depression, anger, irritability, mania, anxiety, somatic symptoms, attention deficit, suicidality, psychosis, sleep disturbances, stereotypical thoughts and behaviors (obsessions and compulsions) and substance use. Each item questions the degree (or the frequency) of disturbance due to a specific symptom during the last 2 weeks. CCSS-5 was found to be a reliable and valid scale in Turkish sample [35].

Pediatric Quality of Life Questionnaire (PedsQL): Varni et al. (1999) developed this quality of life scale to evaluate the physical and psychosocial life experiences of children and adolescents between ages 2-18 independent of their illnesses [36]. It consists of 23 items and results in 3 domain scores such as; physical well-being score, psychosocial well-being score and questionnaire total score. Study done by Çakin-Memik et al. (2007) confirmed the reliability and validity of PedsQL in Turkish language [37].

Procedure

Psychoeducational interventions were applied to PE+ group on the very first interview (T_0) and cases did not receive

any additional briefings during the follow-up interviews (T₁, T₂ and T₃) regarding the topics discussed on T₀. Psychoeducational interview was designed as a short (15-20 minutes), face-to-face psychoeducational briefing made by a child and adolescent psychiatrist, going beyond the regular information given in routine out-patient interview and discussing the topics of manic/hypomanic/depressive episodes, risk groups for mood disorders, suicide, psychosis and psychosocial arrangements (including coping strategies, problem solving and communication skills) for high-risk children. It was administered to both parents in a session separate from the child. A booklet summarizing the key points of the psychoeducational briefing was also given to the parents in order to establish some sort of maintenance for the psychoeducational information and make sure they can double-check if they did not understand some parts during the interview.

Statistical Analysis

The data was analyzed using the Social Sciences software version 21.0 (SPSS Inc. Chicago, IL, USA). Kolmogorov-Smirnov test was used to assess whether the data fit normal distribution. Chi-square test was performed in order to assess the differences of categorical variables between groups. In the analysis of paired groups; an Independent T-test was used for normally or Mann-Whitney U test (MWU) was used for non-normally distributed data. Repeated Measures ANOVA test was used to compare estimated marginal means of variables between groups on each time point (T₀-T₃). Mauchly's Tests of Sphericity was utilized in order to determine if the data violated the rules of sphericity or not. Greenhouse-Geisser correction was used for non-spheric variables in the Repeated Measures ANOVA analysis. The value of p<0.05 was accepted as statistically significant.

RESULTS

Ages of PE+ group ranged between 10.58 and 17.58 years (mean[±SD]=14.80[±2.56]) and PE - group ranged between 10.83 and 17.25 years (mean[±SD]=13.83[±2.33]). There was no statistically significant difference between groups regarding age (Z=-1.666, p=0.096, MWU test). All of the explored continuous data were non-normally distributed and median values and inter-quartile ranges are given in Table 1. There were no significant difference between groups regarding gender [χ²(1,N=60)=0.635, p=0.426], type of BD among parents (p=0.426, Fisher's Exact Chi-square test) and psychiatric diagnosis throughout the follow-ups [χ²(1,N=60)=1.111, p=0.292]; but the majority of the parents with BD diagnosis in PE - group were mothers [χ²(1,N=60)=10.756, p=0.002] (Table 1). Regarding the psychiatric symptoms and quality of life throughout the study (T₀-T₃); only somatic symptoms (F=16.809, p<0.001, Repeated Measures ANOVA) and manic symptoms (F=3.257, p=0.026, Repeated Measures ANOVA) subscale scores in CCSS-5 showed significant difference between PE+ and PE - groups (Table 2). Even though both groups showed an increase in somatic and manic symptoms on interviews T₁ and/or T₃; overall reduction in symptom severity was more

distinct for PE+ group (Figure 2 and 3).

Table 1. Sociodemographic and psychiatric features of the participants.

	Mean (±SD)		Z	p*
	PE+ Group	PE - Group		
Age - years	14.80 (±2.56)	13.83 (±2.33)	-1.666	0.096
	Number of Cases (%)		χ ²	p†
	PE+ Group	PE - Group		
Gender			0.635	0.426
Male	20 (66.67%)	17 (56.67%)		
Female	10 (33.33%)	13 (43.33%)		
Parent with BD			10.756	0.002
Diagnosis				
Mother	17 (56.67%)	28 (93.33%)		
Father	13 (43.33%)	2 (6.67%)		
Type of BD Among Parents			-	0.112‡
Type I	26 (86.67%)	30 (100.00%)		
Type II	4 (13.33%)	-		
Psychiatric Diagnosis Throughout the Follow-ups			1.111	0.292
Presented	14 (46.67%)	10 (33.33%)		
Did not present	16 (53.33%)	20 (66.67%)		

SD, standard deviation; PE+, group who received psychoeducational intervention; PE-, group who did not receive psychoeducational intervention; BD, bipolar disorder; * Mann-Whitney U test, statistically significant p values are written in bold. † Chi-square test, statistically significant p values are written in bold. ‡ Fisher's Exact Chi-square test, statistically significant p values are written in bold.

Table 2. Comparison of psychiatric symptoms and quality of life between groups throughout the follow-up interviews.

		Mauchly's Test of Sphericity	Repeated Measures ANOVA*	
		p	F	p
DSM-5 Level 1 Cross-Cutting Symptom Scale Child Form	Somatic Symptoms	0.151	16.809	<0.001
	Sleep Disturbances	<0.001	1.002	0.355
	Attention Deficit	0.001	1.750	0.181
	Depressive Symptoms	0.001	0.414	0.669
	Anger	0.216	2.313	0.082
	Irritability	0.003	1.490	0.234
	Manic Symptoms	0.594	3.257	0.026
	Anxiety Symptoms	<0.001	0.701	0.505
	Psychotic Symptoms	<0.001	0.106	0.885
PedsQL	Stereotypical Symptoms (Obsessions/Compulsions)	<0.001	1.485	0.236
	Physical Well-being	<0.001	2.061	0.151
	Psychological Well-being	<0.001	1.639	0.206
	Total	<0.001	2.190	0.134

PedsQL: Pediatric Quality of Life Inventory. * Greenhouse-Geisser correction for violation of sphericity was used for non-spheric variables. Statistically significant p values are written in bold.

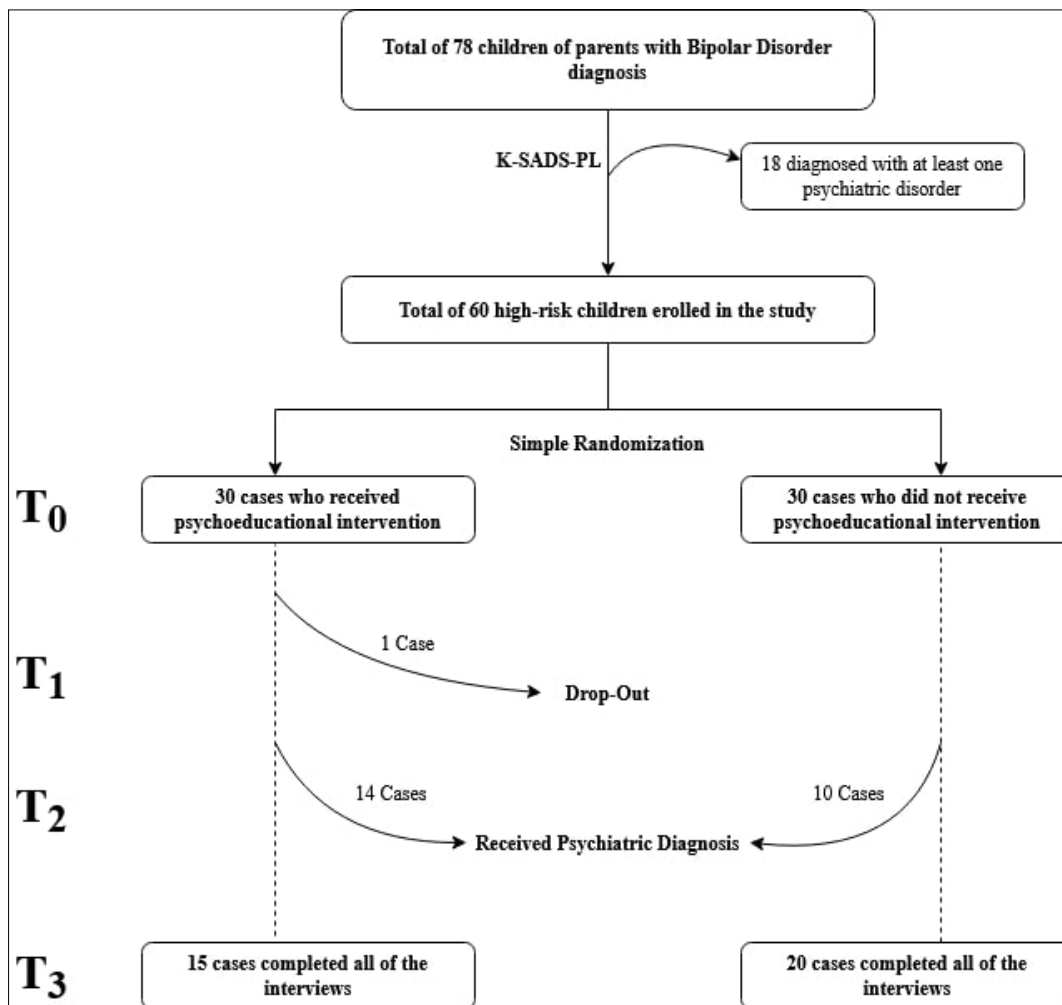


Figure 1. Flow diagram of data collection and the execution of the research.

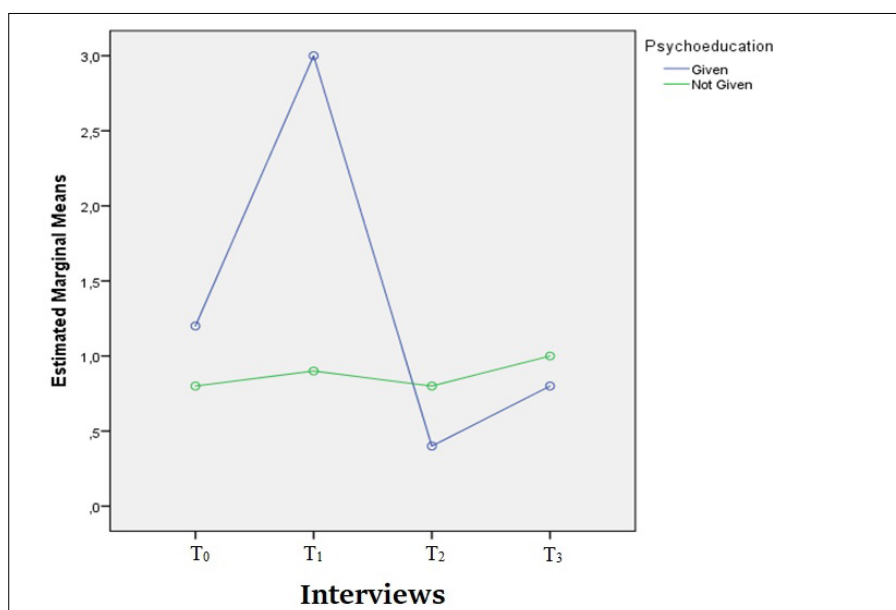


Figure 2. Investigation of the estimated marginal means for somatic symptom subscale of DSM-5 Level 1 Cross-Cutting Symptom Scale Child Form through-out the study period on each interview (T₀ - T₃).

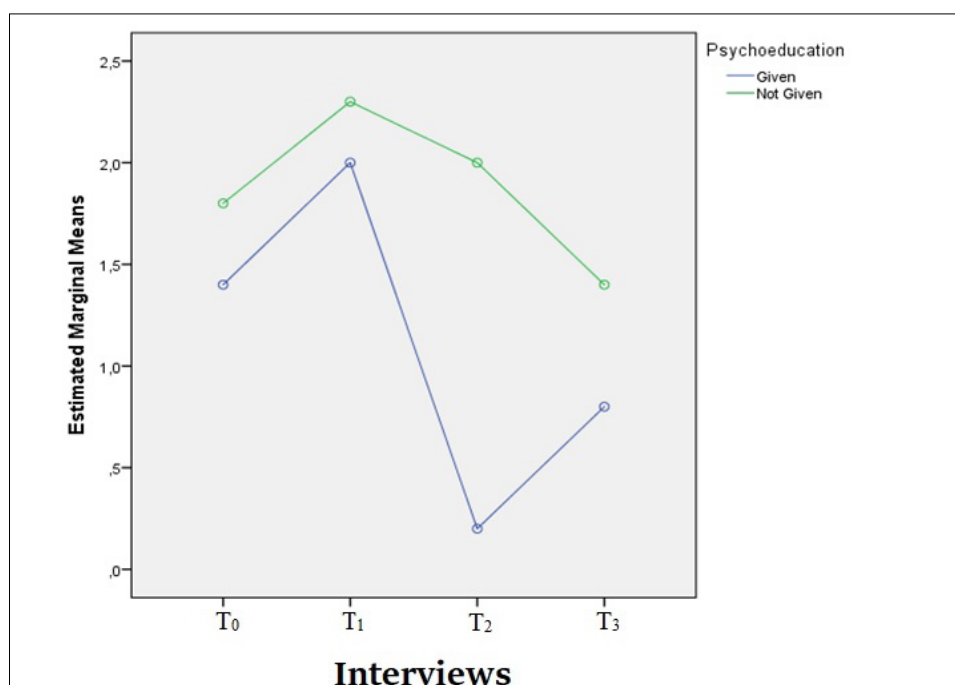


Figure 3. Investigation of the estimated marginal means for manic symptom subscale of DSM-5 Level 1 Cross-Cutting Symptom Scale Child Form through-out the study period on each interview (T₀ - T₃).

DISCUSSION

The purpose of this study was to investigate the effects of psychoeducational interventions on the symptomatology and quality of life of asymptomatic HR youth. Even though quality of life and most of the symptom groups in CCSS-5 did not differ between PE+ and PE - groups; overall reduction in somatic and manic symptom severity was more distinct for PE+ group. To an extent, results from previous research done with symptomatic HR group seem to be in line with the effects of psychoeducation on asymptomatic HR that we found in our study. Especially, improvement in affective symptomatology with CBT and longer remission periods with FFT can be explored in the same scope with the overall reduction in manic symptom severity we showed in PE+ group [23,25].

Nevertheless, improvement in somatic symptomatology that we demonstrated in PE+ should be approached from a different angle. Family interaction is reciprocal, which means that one person's behavior has effect on the behavior of others in the family [38,39]. In addition, studies conducted on BD patients frequently report family relationships as a leading source of life stress [40]. In such families, especially if there is a parent with chronic psychiatric disorder (i.e. BD), children might not get proper attention for their emotional distress; but they might gain attention for their physical symptoms which follow an emotional disturbance. For the children, these reactions might establish a way of thinking which translates as somatic complaints are more acceptable than the expression of strong feelings [41]. In line with this point of view, overall reduction in somatic

symptom severity of PE+ group that we found might be due to the positive effect of psychoeducation on family communication and problem solving skill (psychoeducation that we utilized included sections about coping strategies, problem solving and communication skills). However, there is no previous research indicating the presence of somatic symptoms/somatization disorders among HR youth; so whether somatic symptoms are the consequences of family conflict or a core component of prodromal phase of BD is still unclear. It should also be highlighted that, previous studies done among symptomatic HR did not utilize well-structured symptom screening tools which examines all of the psychiatric symptom clusters according to DSM-5 [23,25]. Therefore we were unable to provide a thorough discussion about why we only could find positive effects on manic and somatic symptom clusters but not others; so it is clear that further studies using both psychoeducational interventions and symptom screening tools based on DSM-5 are needed to be done in HR group in order to fully clarify the effectiveness of psychoeducation.

This was the first study to explore the effectiveness of prevention strategies in an asymptomatic HR sample, which can be regarded as the most important strength of our study. However it still has some limitations to some extent. Firstly, even though previous studies on symptomatic HR group were done in samples with similar sizes, we could not perform a power analysis and our sample size might be regarded as small. Secondly, performing a randomization but not being able to "blind" the participants may be counted as a limitation. Thirdly, due to the design of the study we had to exclude the participants who got diagnosed

with psychiatric disorders throughout the follow-up period; so we could not determine the absolute effect of psychoeducation on the whole sample. Also by definition asymptomatic HR youth did not have disturbances in global functioning and clinical symptomatology; so we had to use self-report scales instead of objective clinical assessment tools.

In conclusion, psychoeducational and psychosocial interventions have been found effective for symptom management and mood episode prevention among symptomatic HR youth; but strategies in asymptomatic HR group were never explored before. In the light of previous studies indicating that psychological interventions are more effective in the early stages of BD compared with the later stages; asymptomatic HR youth is an important and critical population for prevention strategies. Further studies with prospective designs which focus on the intervention strategies in asymptomatic HR youth are needed to fully benefit from this early and valuable stage in the psychopathological pathway of BD.

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REFERENCES

- [1] Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry* 2011;68(3):241-251.
- [2] Van Meter AR, Moreira ALR, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry* 2011;72(9):1250-1256.
- [3] Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry* 2014;204(2):122-128.
- [4] Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, et al. Toward the definition of a bipolar prodrome: Dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry* 2016;173(7):695-704.
- [5] Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord*. 1994;31(4):281-294.
- [6] Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry* 2004;55(9):875-881.
- [7] Perlis RH, Dennehy EB, Miklowitz DJ, Delbello MP, Ostacher M, Calabrese JR, et al. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: Results from the STEP-BD study. *Bipolar Disord*. 2009;11(4):391-400.
- [8] Post RM, Leverich GS, Kupka RW, Keck PE, McElroy SL, Altshuler LL, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. *J Clin Psychiatry* 2010;71(7):864-872.
- [9] Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB et al. Diagnostic Precursors to Bipolar Disorder in Offspring of Parents With Bipolar Disorder: A Longitudinal Study. *Am J Psychiatry* 2015;172(7):638-646.
- [10] Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. *J Affect Disord*. 2010;121(1-2):127-135.
- [11] Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63(2):175-183.
- [12] Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, et al. Switching from 'Unipolar' to Bipolar II: An 11-Year Prospective Study of Clinical and Temperamental Predictors in 559 Patients. *Arch Gen Psychiatry* 1995;52(2):114-123.
- [13] Kochman FJ, Hantouche EG, Ferrari P, Lancrenon S, Bayart D, Akiskal HS. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *J Affect Disord*. 2005;85(1-2):181-189.
- [14] Geller B, Cooper TB, Zimmerman B, Frazier J, Williams M, Heath J, et al. Lithium for prepubertal depressed children with family history predictors of future bipolarity: A double-blind, placebo-controlled study. *J Affect Disord*. 1998;51(2):165-175.
- [15] Miklowitz DJ, Chang KD, Taylor DO, George EL, Singh MK, Schneck CD, et al. Early psychosocial intervention for youth at risk for bipolar I or II disorder: A one-year treatment development trial. *Bipolar Disord*. 2011;13(1):67-75.
- [16] Miklowitz DJ, Schneck CD, Walshaw PD, Singh MK, Sullivan AE, Suddath RL, et al. Effects of Family-Focused Therapy vs Enhanced Usual Care for Symptomatic Youths at High Risk for Bipolar Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2020;77(5):455-463.
- [17] Vallarino M, Henry C, Etain B, Gehue LJ, Macneil C, Scott EM, et al. An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. Vol. 2, *The Lancet Psychiatry* 2015;2(5),548-563.
- [18] Ekhtiari H, Rezapour T, Aupperle RL, Paulus MP. Neuroscience-informed psychoeducation for addiction medicine: A neurocognitive perspective. In: *Progress in Brain Research*. Elsevier B.V.; 2017. p. 239-64.
- [19] Cardamone-Breen M, Jorm A, Lawrence K, Rapee R, Mackinnon A, Yap M. A Single-Session, Web-Based Parenting Intervention to Prevent Adolescent Depression and Anxiety Disorders: Randomized Controlled Trial. *J Med Internet Res*. 2018;20(4):e148.
- [20] González-Bueso V, Santamaría J, Fernández D, Merino L, Montero E, Jiménez-Murcia S, et al. Internet Gaming Disorder in Adolescents: Personality, Psychopathology

- and Evaluation of a Psychological Intervention Combined With Parent Psychoeducation. *Front Psychol.* 2018;9:787.
- [21] Banaschewski T, Becker K, Döpfner M, Holtmann M, Rösler M, Romanos M. Attention-Deficit/Hyperactivity Disorder. *Dtsch Arztebl Int.* 2017;114(9):149-159.
- [22] Bevan Jones R, Thapar A, Stone Z, Thapar A, Jones I, Smith D, et al. Psychoeducational interventions in adolescent depression: A systematic review. *Patient Educ Couns.* 2018;101(5):804-816.
- [23] Miklowitz DJ, Schneck CD, Singh MK, Taylor DO, George EL, Cosgrove VE, et al. Early intervention for symptomatic youth at risk for bipolar disorder: A randomized trial of family-focused therapy. *J Am Acad Child Adolesc Psychiatry* 2013;52(2):121-131.
- [24] Goldstein TR, Fersch-Podrat R, Axelson DA, Gilbert A, Hlastala SA, Birmaher B, et al. Early intervention for adolescents at high risk for the development of bipolar disorder: Pilot study of interpersonal and social rhythm therapy (IPSRT). *Psychotherapy* 2014;51(1):180-189.
- [25] Leopold K, Bauer M, Bechdolf A, Correll CU, Holtmann M, Juckel G, et al. Efficacy of cognitive-behavioral group therapy in patients at risk for serious mental illness presenting with subthreshold bipolar symptoms: Results from a prespecified interim analysis of a multicenter, randomized, controlled study. *Bipolar Disord.* 2020. DOI: [10.1111/bdi.12894](https://doi.org/10.1111/bdi.12894)
- [26] Nadkarni RB, Fristad MA. Clinical course of children with a depressive spectrum disorder and transient manic symptoms. *Bipolar Disord.* 2010;12(5):494-503.
- [27] Benarous X, Consoli A, Milhiet V, Cohen D. Early interventions for youths at high risk for bipolar disorder: a developmental approach. *European Child and Adolescent Psychiatry* 2016;25(3): 217-233.
- [28] Pfennig A, Leopold K, Bechdolf A, Correll CU, Holtmann M, Lambert M, et al. Early specific cognitive-behavioural psychotherapy in subjects at high risk for bipolar disorders: Study protocol for a randomised controlled trial. *Trials.* 2014;15(1):161.
- [29] Reinares M, Sánchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: What, for whom, and when. *J Affect Disord.* 2014;156: 46-55.
- [30] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36(7):980-988.
- [31] Gokler B, Unal F, Pehlivanurk B, Kultur E, Akdemir D, Taner Y. Reliability and Validity of Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T). *Turk J Child Adolesc Ment Heal.* 2004;11(3):109-116.
- [32] InalEmiroglu N, Karaarslan D. Psychoeducational Therapy of Mood Disorders in Children and Adolescents - Parent Version. Ankara, Turkey: Turkish Association for Child and Adolescent Psychiatry Publishing; 2016.
- [33] West AE, Pavuluri MN. Psychosocial Treatments for Childhood and Adolescent Bipolar Disorder. *Child Adolesc Psychiatr Clin N Am.* 2009;18(2):471-482.
- [34] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Arlington, VA; 2013.
- [35] Yalin Sapmaz S, Ozek Erkuran H, Kavurma C, Ozturk M, Uzel Tanriverdi B, Koroglu E, et al. Validity and Reliability of DSM-5 Level 1 Cross-Cutting Symptom Scale Turkish Version (Child Form for 11 - 17 Years and Parent Form for 6 - 17 Years). *Anatolian Journal of Psychiatry* 2017;18(2):99-106.
- [36] Varni JW, Seid M, Rode CA. The PedsQL™: Measurement model for the pediatric quality of life inventory. *Med Care* 1999;37(2):126-139.
- [37] Cakin-Memik N, Agaoglu B, Coskun A, Uneri O, Karakaya I. The Validity and Reliability of the Turkish Pediatric Quality of Life Inventory for Children 13 - 18 Years Old. *Turkish Journal of Psychiatry* 2007;18(4):353-363.
- [38] Cook WL, Kenny DA, Goldstein MJ. Parental Affective Style Risk and the Family System: A Social Relations Model Analysis. *J Abnorm Psychol.* 1991;100(4):492-501.
- [39] Salinger JM, O'Brien MP, Miklowitz DJ, Marvin SE, Cannon TD. Family communication with teens at clinical high-risk for psychosis or bipolar disorder. *J Fam Psychol.* 2018;32(4):507-516.
- [40] Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. *J Affect Disord.* 2007;99(1-3):37-44.
- [41] Silber TJ, Pao M. Somatization Disorders in Children and Adolescents. *Pediatr Rev.* 2003;24(8):255 LP - 264.