

## THEME ARTICLES:

### Pediatric Bipolar Disorders: From the Perspective of Turkey

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#### ABSTRACT

**Introduction:** In Turkey, there is much controversy and skepticism about the existence of mania in children and adolescents, and a paucity of rigorous data. Despite ongoing controversy, the view that pediatric Bipolar Disorder (BD) is rare or non-existent has been increasingly challenged not only by case reports but also by systematic research. **Methods:** *Diagnostic and Statistical Manual for Mental Disorders* (DSM) criteria are usually employed in these research studies and case reports and it was strongly suggested that pediatric BD may not be rare but that it may be difficult to diagnose. **Results:** In concordance with the current literature, euphoric mood and episodic course is rare in Turkish children and adolescents and the affective phenomenology is often mixed and dysphoric, with affective storms and temper outbursts. Comorbidity (especially with ADHD) is a big issue in accurate diagnosis and treatment. **Conclusion:** There are promising treatment studies, but we need more studies in both pre-pubertal children and adolescents about phenomenology, etiology, and treatment of this important condition.

**Key words:** bipolar disorder, children, Turkey

#### RÉSUMÉ

**Introduction:** La manie chez les enfants et adolescents, en Turquie, fait l'objet de peu de données rigoureuses, et il existe une grande controverse et beaucoup de scepticisme quant à sa réalité et à ses manifestations. Malgré la controverse actuelle, l'opinion selon laquelle le trouble bipolaire pédiatrique est rare ou inexistant est de plus en plus contestée, non seulement par la publication d'études de cas, mais aussi par les résultats de recherche systématique. **Méthodologie:** Les travaux de recherche et les études de cas – qui utilisent généralement les critères du *Diagnostic and Statistical Manual for Mental Disorders* (DSM) – laissent fortement penser que le trouble bipolaire pédiatrique n'est peut-être pas si rare que l'on croit, mais qu'il est difficile à diagnostiquer. **Résultats:** Comme l'indique la littérature actuelle, l'humeur euphorique et la récurrence sont rares chez les enfants et adolescents turcs; la phénoménologie affective est souvent mixte et dysphorique, avec des marques excessives d'affection et des explosions de colère. La comorbidité (notamment avec le TDAH) complique singulièrement le diagnostic et le traitement. **Conclusion:** Les études sur le traitement du trouble bipolaire sont prometteuses, mais il est nécessaire disposer de plus de données sur la phénoménologie, l'étiologie et le traitement de cette maladie grave chez les enfants prépubertaires et les adolescents.

**Mots-clés:** trouble bipolaire, enfants, Turquie

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#### Introduction

Turkey has a population of 65 million, of which children and adolescents make up 30.6% of the general population (General Statistics of Ministry of Internal Affairs and State Institute of Statistics 2001). After the collapse of the Ottoman Empire, the Turkish Republic emerged in 1923. Since then, rapid economic and social changes have initiated migration from rural to urban areas, reversing the nation's urban/rural population ratio (now at 70% vs 30%). The Turkish population is also culturally and ethnically diverse. Turkey has been a part of European Common Market since 1940s and has been negotiating with European Union for full membership. The Turkish Republic is the only country that lies on both Europe and Asia and is the only secular and democratic country in the world which consist of mainly muslim

population (Yazgan 1997).

Bipolar disorder (BD) in childhood had not been diagnosed with any regularity until recently (Biederman et al. 2003). Despite ongoing controversy, the view that pediatric BD is rare or non-existent has been increasingly challenged not only by case reports but also by systematic research (Geller et al. 2004, Lewinshon et al. 1995). Research studies in Turkey and in other countries strongly suggest that pediatric BD may not be rare but that it may be difficult to diagnose (Biederman et al. 2003). Historically, several factors have made the accurate diagnosis of BD in childhood difficult, including: lack of awareness; diagnostic confusion (Mohr 2001); clinical bias against the diagnosis of mania in children; low base rate of disorder; symptom overlap between BD and other more prevalent childhood-onset psychiatric disorders; and

developmental constraints and variability in clinical presentation (Sanchez et al. 1999). Kennedy et al. (2004) reported that significant ethnic differences in clinical presentation of BD underlines the need for further assessment and treatment of bipolar children with different ethnic and cultural origins. According to a review which evaluated the epidemiology of BD in children and adolescents in non-US samples, the ICD-10 and DSM-IV differences in diagnostic criteria and different levels of recognition of Child and Adolescent Psychiatry as a true specialty in Europe may lead to clinician bias against BD. Controversy exists whether there is true higher prevalence of pediatric BD in the USA. US–International differences may be a methodological artifact and research is needed in this field (Soutullo et al. 2005). These results revealed the trans-Atlantic controversy and differences in pediatric BD diagnosis.

### **Phenomenological studies of Pediatric BD in Turkish population**

Though childhood mania has been known as a distinct disorder, this diagnosis was rarely used by clinicians until recently (Diler 2007). The issue is not merely nosological; a correct diagnosis has important implications in preventing and treating the disorder (Biederman et al. 1999). A phenotypic classification is needed because of various symptomatologic spectrum (Leibenluft et al. 2003). Therefore, evaluating age of onset at clinical presentations has been useful for providing accurate diagnosis. Turkish clinicians are closely following international discussions about diagnostic challenges of pediatric BD (Diler and Emiroglu 2007). Accordingly to this, recent diagnostic instruments were translated into Turkish and evidence supporting the instrument's reliability and validity in the Turkish population are still being provided. Affective module of Washington University at St. Louis - Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS- Present state and lifetime-for DSM-IV) (Geller et al. 1996) was translated into Turkish and it is used by Turkish clinicians when making diagnoses of mood disorders (Emiroglu et al. 2002). The Schedule for Affective Disorders and Schizophrenia for School Age children-present and lifetime version (KSADS-PL) (Kaufman et al. 1997) was also translated into Turkish. Its reliability and validity in the Turkish population are being provided and it can be used for diagnosis and differential diagnosis of mood disorders by Turkish clinicians. Child Behavior Checklist (CBCL) 4-18 and Parent-Young Mania Rating Scale (P-YMRS) are being used in Turkish children and adolescents with and without BD (Gökler et al. 2004).

There is only one available epidemiologic study in

Turkish children with BD and this study is the first report in the literature of manic symptomatology in prepubertal children. Diler et al. (2008) screened 2468 children aged between 7 and 12 by using the Parent-Young Mania Rating Scale (P-YMRS). Among 10220 children, subjects were included through a random selection of 3rd, 4th, and 5th grade classes from all available elementary schools in Adana city, Turkey. According to the results, P-YMRS score was 17 or higher ("probable-mania") in 5.9% of the children (n=146) and was 27 or higher ("mania") in 1.1% of the children (n=27). According to this study, the most common manic symptoms on the P-YMRS in all children were elevated mood (5.5%), increased motor activity (energy; 4.7%), poor insight (4.2%), sleep problems (1.5%), poor appearance (poor hygiene, poor or odd grooming; 1.5%), rapid thoughts / flight of ideas (0.9%), problems with thought content (0.9%), being talkative / pressured speech (0.7%), sexual interest (0.6%), irritability (0.4%), and disruptive / aggressive behavior (0.4%). Being talkative/pressured speech, increased motor activity (high energy), elevated mood, sleep problems, rapid thoughts / flight of ideas, and irritability were the symptoms with the highest mean P-YMRS scores in the mania group. Although a clinical interview was not conducted in this study, it provided data to confirm in Turkish children that a cut-off score of 17 on total P-YMRS is efficient and a cut-off score of 27 on total P-YMRS is specific to differentiate BD from other disorders (Youngstrom et al. 2004). The mean score of all symptoms on the P-YMRS, except for increased motor activity, elevated mood, and poor insight, were significantly higher in the mania group than in the probable-mania group. The same study also evaluated the dimensional presentation of the prepubertal children and children with mania had significantly higher scores on all Child Behavior Checklist (CBCL) subscales and CBCL-PBD profile (sum of attention, aggression, and anxiety/depression subscales) compared to the normal group. P-YMRS was significantly correlated with all CBCL scores, including CBCL-PBD score. The highest correlations of P-YMRS were for externalization ( $r = 0.39$ ), total problems ( $r = 0.38$ ), aggression ( $r = 0.38$ ), CBCL-PBD ( $r = 0.38$ ), and thought disorder ( $r = 0.37$ ) scores on the CBCL. These results suggest that the prevalence of BD in prepubertal Turkish children is possibly around 1.1% (Diler et al. 2008).

Diler and Avci (1999) reported first Turkish pediatric bipolar cases that developed mania after treatment with selective serotonin reuptake inhibitors. It was highlighted that clinicians need to be more alert in youth who have a family history of affective disorder and hyperactivity. A case series reported children and adolescents with bipolar phenotype features between 7-15 ages who were

being followed at a university outpatient unit in Turkey (Inal-Emiroglu 2004). The WASH-U-KSADS was used for the assessment of mood disorders diagnoses and symptomatology. The most frequent severe symptoms observed at the end of the assessment were grandiosity, distractibility, and unusual energy. Four of the cases had mixed cycling features. Five of the cases had ultradian cycling features. These results are consistent with available literature (Geller et al. 1998(a), Geller et al. 1998(b), Geller et al. 2002).

It has been difficult to diagnose BD in youth because of developmental discrepancies between adulthood and childhood or adolescence bipolarity (Biederman et al. 2000). Initial reports suggested that classical, adult-like symptomatology of BD, with euphoric mood and episodic course, was rare in children and adolescents (Geller et al. 1997, Carlson et al. 1998), and that the affective phenomenology is often mixed; dysphoria, with affective storms and temper outbursts, is much more frequent than euphoria (Wozniak et al. 1995(a), Geller et al. 2000); however, recent findings from US report otherwise. Inal-Emiroglu et al. (2008)(a) reported a naturalistic follow-up case series, which was only a preliminary clinical data assessment of children and adolescents with bipolar spectrum disorders. The study sample consisted of 27 consecutive admissions to the Child and Adolescent Psychiatry Clinic between 2002 and 2006. The WASH-U-KSADS was administered to mothers for an assessment of the problem of their children and to children about themselves. The authors conducted a pilot study with a small group and found some phenomenological differences between episodic and non-episodic patients, episodic patients were more likely to have psychotic features and to have a later age of onset. Episodic group consisted of adolescents mostly, so they observed more frequent psychotic symptoms than the others (Inal-Emiroglu et al. 2008(a)).

Previous researchers reported a higher prevalence of psychotic symptoms in patients with BD who became ill at a younger age than in those whose illness occurred later. For that reason, adolescent patients with BD were frequently misdiagnosed with schizophrenia in the past because of severe psychotic symptoms. Erkiran et al. (2003) investigated three groups which consisted of adolescent-onset adolescents (n=60), adolescent-onset adults (n=60) and adult-onset adults (n=60) to investigate the relationship between age of onset and phenomenology of BD in Turkish population. All diagnoses were made according to the DSM IV BD criteria. Adolescent-onset adolescents and adolescent-onset adults were different from adult-onset patients with respect to mixed episodes (26.7% vs 15%), mood congruent or incongru-

ent psychotic features (35% vs 50%, 31.7% vs 66.7%), and length of hospitalization (23.9±4.8 vs 23.8±3.9). This study put forward the hypothesis that adolescent-onset mania may be a different subtype than adult-onset mania considering type of episode, phenomenology, and other clinical features in Turkish patient population (Erkiran et al. 2003).

### Turkish Bipolar offspring studies

One thing we know with absolute certainty is that the children of patients with BD are at high risk for developing the same illness (Gershon et al. 1982, Lapalme et al. 1997, Chang et al. 2000). Therefore, one might expect to see elevated rates of either syndromal presentation or prodromal symptoms in bipolar offspring when examined during the childhood. A detailed evaluation of mood symptomatology is also suggested in order to identify prodromal manifestations of mania in the bipolar offspring (Delbello et al. 2001). Studies with offsprings may also be useful to define predictors of psychopathology. According to a offspring study in the US, children of bipolar parents had an elevated risk for developing bipolar and other psychiatric disorders (Singh et al 2007). Inal-Emiroglu et al. (2008(b)) investigated the frequency and subsyndromal symptoms of mood and disruptive behavior disorders in the offspring of a group of Turkish parents with bipolar I illness in comparison with the offspring of healthy parents. They used the WASH-U-KSADS for the assessment of mood disorders diagnoses and symptomatology (i.e., start and end of each mania symptoms). It was concluded that the offspring of bipolar parents had a 9.48 fold higher risk of receiving a psychiatric diagnosis than did the offspring of the healthy parents. While only two children of bipolar parents were diagnosed as having a mood disorder, others (30.9%) displayed mild and severe manic or depressive or a disruptive behavior symptoms (20%). The rate of mood symptoms was significantly higher in the probands than in the controls (case n=21, 30.9%, control n=6, 8.8%). Severe and mild depressive symptoms were more frequent than mania symptoms in the offspring of bipolar parents. Results from this pilot study indicated that children of bipolar I parents may have significantly higher rates of psychiatric symptoms at both the syndromal and subsyndromal levels than do the children of healthy controls (Inal-Emiroglu et al. 2008(b)). Singh's et al. (2007) used the same diagnostic instrument (WASH-U-KSDAS) in a bipolar offspring group and they found that bipolar offspring group more frequently met subsyndromal criteria for at least one Axis I diagnosis compared to the control offspring. However, no statistically significant group differences in subsyndromal scores of mood or anxiety disorders. Therefore, bipolar

offspring groups are very useful to identify potential prodromal manifestations of the disorder and to eventually establish targeted early intervention strategies and similar results were obtained from different cultural origins.

Akdemir et al. (2007) reported another Turkish bipolar offspring study, their patient population consisted of thirty-six children of 28 bipolar I parents and 33 children of 28 control parents between the ages of 6 and 17. Bipolar parents and all of the children were screened by using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (KSADS-L) (Endicott And Spitzer 1978) and the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL), respectively. The spouses of bipolar parents completed Symptom Checklist-90-Revised (SCL-90-R) and the children completed Parenting Style Scale (PSS) (Derogatis 1977). The rates of mood disorders and conduct disorders were statistically significantly higher in the children of parents with bipolar disorder compared to the controls. Similar to the previous Turkish offspring study (Inal-Emiroglu et al. 2008(b)), they found that subsyndromal depressive symptoms were more frequent bipolar offspring group. In terms of parents' attitudes, offspring group has statistically significant lower scores in psychological otonomy subscale points in PSS (Akdemir et al.2007).

It was suggested that the children of parents with BD can be called as a high risk group in which early diagnosis and intervention are very important. The fact that the disruptive behavior disorders and mood symptoms are usually diagnosed in the early stage, these children should cautiously be examined to rule out BD. Observing these children longitudinally might prove to be beneficial in establishing the criteria for early diagnosis and intervention (Diler RS and Inal-Emiroglu 2007).

### **Pediatric BD and other comorbid psychiatric disorders in Turkish population**

There is a considerable overlap between diagnostic criteria for mania and disruptive behavioral disorders, particularly ADHD. The overlapping diagnostic boundaries need to be better described. The chronic course and the overlap of symptoms, such as hyperactivity, impulsivity/aggressiveness, distractibility, and emotional lability, the differential diagnosis among early-onset mania, severe ADHD, CD with affective dysregulation is often very difficult especially when there is a co-occurrence of two or three of these disorders (Carlson et al. 2000, Oner et al. 2002) evaluated the psychiatric diagnoses of adolescent cases whose primary complaint was attention problems and they found that ADHD and major depression were the

most frequent diagnoses in outpatients with attention problems. For these reasons, detailed assessment is needed in terms of differentiating mood disorders from ADHD in this population. In the light of recent data, Turkish clinicians have been discussing in forums about how to make an accurate diagnosis in mixed conditions (Oner et al.2002).

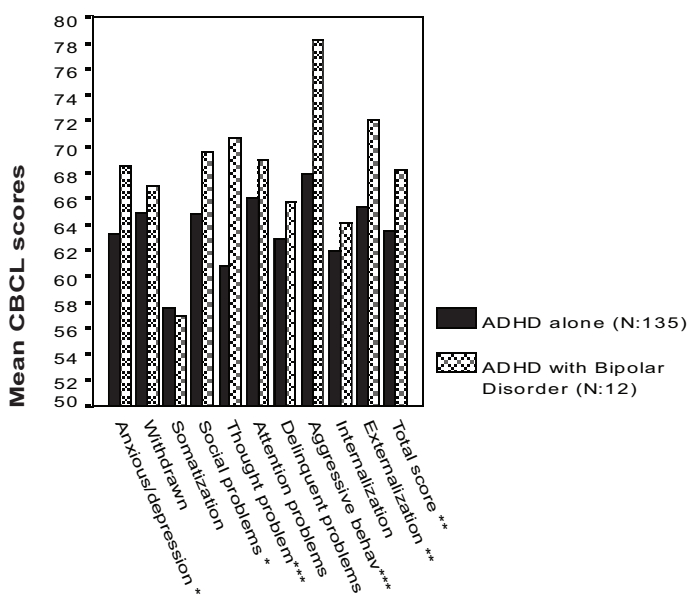
Diler et al. (2007) evaluated one hundred forty-seven treatment- and drug-naive children, aged 7 and 13 years who had been consecutively referred to the ADHD clinic by K-SADS-PL. Parents also completed CBCL 4-18 and P-YMRS prior to the clinical interview. There were twelve ADHD children (8.2%) with comorbid BD (ADHD+BD). Gender was not significantly different between the two groups. ADHD children with comorbid bipolar (ADHD+BD) were significantly older than those without BD ( $11.25\pm 0.87$  vs.  $10.11\pm 0.53$ ). ADHD+BPD group had significantly higher rates of depressive disorders, oppositional defiant disorder, panic disorder, and family history of BD compared to ADHD group. Anxiety disorders in ADHD+BD includes 2 cases with both generalized anxiety disorder and social phobia, and 3 cases with panic disorder. ADHD+BD group had significantly more problems on CBCL (anxious/depressed, social problem, thought problem, aggression, externalization, and total score) (Figure 1.) and on P-YMRS (all items except insight) compared to the ADHD group. These findings in Turkish prepubertal children findings are consisted with the growing body of literature in children with BD. The most of the patients did not have full blown manic episode. Seven patients (58.3%) in ADHD+BD had BD Not Otherwise Specified (BPD-NOS, 57.1% of the were rapid cycling), 4 patients (33.3%) had BD type I with mixed episode (75% of them were rapid cycling), 1 (8.3%) patient with BD type I with manic episode. Seven patients (58.3%) in all group had rapid cycles. None of them had any psychotic symptom (Diler et al. 2007).

CBCL has been reported to differentiate between comorbid and non-comorbid ADHD in children on Delinquent Behavior, Aggressive Behavior, Somatic Complaints, Anxious/Depressed, and Thought Problems scales of CBCL (Biederman et al. 1995) and distinguish pediatric BD from ADHD subjects on Aggression, Attention Problems, and Anxious/Depresses scales of CBCL (Mick et al. 2003). Consisted with the most of the above literature Diler et al.(2007) reported that Turkish children with ADHD+BD had higher anxious/depressed, social problem, thought problem, aggression, externalization, and total score on CBCL; however CBCL can be used for assessment of BD children but should not be used to make th BD diagnosis. Diler et al. (2008) searched for clinical correlations and used logistic regression to show

how well each CBCL subscale predicted the presence of mania and probable-mania, after adjusting for any demographic differences. Elevated mood, increased activity levels, and poor insight were the most frequent manic symptoms in this sample. Children with probable-mania and mania had higher scores on all CBCL subscales and the CBCL-Pediatric Bipolar Disorder (CBCL-PBD) profile (sum of attention, aggression, and anxiety / depression subscales). Logistic regression analysis revealed only thought problems on CBCL that predicted probable-mania and mania (Diler et al. 2008).

The recent consensus that prepubertal and early adolescent onset mania may occur more frequently than it was previously recognized has led to greater attention to BD in children and overlapping symptoms between ADHD and BD such as motor hyperactivity, abnormally increased energy, and distractibility. In recent studies, mania criteria specific to BD (e.g., elated mood and/or grandiosity as one of the mania/hypomania criteria) are proposed to distinguish pediatric BD from ADHD (Geller et al. 1998(a), Geller et al. 2000, Geller et al. 1998(b), Geller et al. 2002). Similarly, Geller et al. 1998(a) reported that prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms such as grandiose delusions. Authors concluded that it is possible to diagnose prepubertal BD with comorbid ADHD. Similar to these findings, Oner and Kılıc (2000) reported two pediatric cases in Turkey: One of them had severe mood lability during a day and the other showed exaggerated hypersexual behaviors. They concurred with Dr. Geller's conclusion that these symptoms may be discriminative for BD. Diler et al.'s (2007) study also supported Geller et al.'s conclusion and they reported that P-YMRS scores (Elevated mood, Increased motor activity/Energy, Sexual interest, Sleep disturbance, Irritability, Speech, Thoughts, Content, Disruptive/ aggressive behavior, Appearance) were significantly high in ADHD+BD than in ADHD children. Aggression, irritability, elevated mood, and speech were highest P-YMRS scores in ADHD+BD group and significance level was higher on aggression, elevated mood, sexual interest, sleep disturbance, and thought items. In a recent study, which compared six screening instruments including CBCL for bipolar kids aged 5 to 17 years, P-YMRS was the most powerful predictor of bipolarity in children younger than 11 and was slightly more powerful than CBCL in kids aged 11 to 17 (Youngstrom et al. 2004). It is reported that cut-off scores of 11 and 26 are efficient and specific, successively, in order to differentiate BPD from disruptive behavior problems (Youngstrom et al. 2003). Consistent with this report total P-YMRS score was  $23.92 \pm 4.27$  in ADHD+BPD group versus  $10.43 \pm 6.28$  in ADHD group in this study in Turkey (Diler et al. 2007).

**Figure 1. Comparison of the mean Child Behavior Checklist (CBCL) scores between children with attention deficit hyperactivity disorder (ADHD) and those with comorbid BD (ADHD+BPD)** (adapted from Diler, R. S. & Inal-Emiroglu, F. N. 2007. *Pediatric Bipolar Disorder a Global Perspective* Diler, R.S. (ed.), *Pediatric Bipolar disorder: From the Perspective of Turkey* (pp.193-215). New York, Nova Science Publisher)



\* :  $p < 0.05$  , \*\* :  $p < 0.01$  , \*\*\* :  $p < 0.001$

In comparison to children with unipolar depression, children with bipolar depression were more likely to have severe depression with suicidality, anhedonia and hopelessness. Bipolar depression is associated with higher levels of psychiatric disorders in first-degree relatives (Wozniak et al. 2004). In Diler et al.'s study, family history of BD was significantly higher in ADHD+BD. Although there were no significance between the two groups in regards to family history of depressive disorder, history of depressive disorder episode in the child was significantly 4.7 times higher in ADHD+BD than in ADHD group which stresses the importance of probing for previous depressive episode when differentiating BD from ADHD (Diler et al. 2007).

Wozniak et al. (1995) reported that 88% of bipolar children had oppositional defiant disorder (ODD). Greene and Doyle (1996) also reported that 20% of children with ODD had BPD and 76% of children with BPD had ODD. Consistent with the above findings there were significantly higher rates of ODD (3.5 times higher) in ADHD+BD group as compared to ADHD group in Turkish sample. It is possible that a subform of ODD linked to BPD (thus dysphoric

ODD) may be identified and consequently could lead to new therapeutic approaches directed at the management of extremely difficult youth with compromised prognoses (Spencer et al. 2001).

A frequent bidirectional association between mania and CD has been seen separately in studies of children with CD, ADHD, and mania (Wozniak et al. 1995(a), Spencer et al. 2001). To further investigate whether BPD and CD are separate disorders, Biederman et al. (1997, 1999) systematically investigated the overlap between mania and CD in a consecutive sample of referred youth and in a sample of ADHD subjects to clarify its prevalence and correlates (Biederman et al. 1997, Biederman et al. 1999). These investigators found that the clinical characteristics of CD were similar in CD subjects irrespective of the comorbidity with BD and, vice versa, BD features were similar in children irrespective of the comorbid diagnosis with CD. In both groups, mania presented with a predominantly irritable mood, a chronic course, and was mixed with symptoms of major depression. These findings strongly suggest that children manifesting symptoms of BD and CD may have both disorders. It was reported that CD was 1.96 times more frequent in ADHD+BD than in ADHD children without statistical significance in Turkish sample of preadolescents (Diler et al. 2007).

In a representative community sample of 1709 adolescents (aged 14-18 years), 37 of 115 subjects (32.2%) meeting DSM-IV criteria for BD or from subthreshold bipolar symptomatology were found to meet criteria for comorbid specific anxiety disorders (Lewinshon et al. 1995). Anxiety disorders and panic disorder was found 25% of ADHD+BD cases in prepubertal Turkish sample and panic disorder significantly 33.3 times higher in ADHD+BD group as compared to ADHD group; however, there were no significance between groups in regard to anxiety disorders (Diler et al. 2007).

The relationship between ADHD and BD is also clear in the pattern of co-prevalence of the two disorders in families. There is strong evidence to suggest that this pattern has a familial, and genetic basis (Borchardt and Bernstein 1995, West et al. 1995). Similarly, in a group of Turkish patients it was reported that family history of BD is ten times more frequent in ADHD+BPD group than in ADHD (Diler et al. 2007).

### **Treatment approaches of pediatric BD in Turkey**

The psychosocial interventions for children and adolescents with BD are available in Turkey (e.g., cognitive behavioral therapy, supportive therapy, family therapy), and Turkish clinicians considered that the disorder should be managed by biopsychosocial treatment approaches. However, medical doctors, given the limited source of

other mental health professionals, have been providing most of these psychotherapies. Private insurance companies have limited role in mental health services in Turkey and physicians are very flexible in choosing available treatment options. Medications like typical and atypical antipsychotic medications, old and newer antidepressants (excluding MAO inhibitors), mood stabilizers, and psychostimulants (short acting methylphenidate and OROS- methylphenidate) or other medications for ADHD (atomoxetine, clonidine) that are available in US and European Union are all available in Turkey (Diler and Inal-Emiroglu 2007).

Despite increasing knowledge about the clinical presentation and phenomenology of juvenile onset BD, pharmacotherapy of this disorder has not well studied. The use of pharmacological agents, however, still based on case reports and studies with small numbers of subjects (Weller et al. 2002). Because of the reports that the use of mood-stabilizing agents such as lithium and atypical antipsychotics (e.g., risperidone and aripiprazole) are promising in children and adolescents with BD, these agents are also frequently used in Turkish mental clinics. Another important and recent issue is that there are differences of treatment response to BD through childhood and adolescence. There also needs to be a considerable effort in understanding the developmental phases of affective disorders in youth. The treatment data about Turkish patient population is limited to just a few case reports in adolescence. We do not have sufficient treatment studies in Turkey yet about pediatric BD (Diler and Inal-Emiroglu 2007).

According to available data, BD in childhood and adolescence is often resistant to treatment (Wozniak et al. 1995(b)). Furthermore, starting with or concomitant antipsychotic treatment at least for 4 weeks has been suggested in acute mania on the basis of high incidence of psychotic symptoms in adolescents (Kafantaris et al. 2001). Therefore, addition of atypical antipsychotics to mood stabilizers should be considered as a viable therapeutic option, when adolescents do not respond adequately to mood stabilizers alone (Erermis and Tamar 2001). Hence, a case report in Turkey suggested benefits of olanzapine as an adjunct to mood stabilizers in the treatment of two adolescents with bipolar I disorder who did have insufficient response to mood stabilizers (Inal-Emiroglu et al. 2001). It was also reported that antipsychotics may be useful as an adjunct to mood stabilisers in bipolar disorder. However, further research is warranted regarding the use of atypical antipsychotics in children and adolescents. Olanzapine was useful for a Turkish pediatric patients with bipolar I disorder; however weight gain is an important issue (Inal-Emiroglu et al.

2006). Risperidone is the most common drug in this group used in Turkish children and all atypical antipsychotic medications either as a monotherapy or in combination with mood stabilizers have also been reported to be effective in the treatment of mania in children and adolescents (Frazier et al. 2001). Güzel et al. (2004) reported the clinical follow up of four cases, with the pre-diagnosis of bipolar disorder who had 'hyperactivity, attention deficit symptoms, suicidal thoughts and nervousness' as initial symptoms that were treated with mood stabilizers. They reported that none of patient has clear DSM-IV manic episode criteria but all of them have brief many manic symptoms and they were treated with valproate successfully (Güzel et al. 2004). According to a naturalistic case series in Turkey, a large number of patients responded to mood stabilizers and antipsychotic agents (89.5%). Mostly, combination treatments (mood stabilizer and atypical antipsychotics) were required (73.7%) in this sample. Olanzapine and mood stabilizers were effective but weight gain was the most frequent side effect in the case group (Inal-Emiroglu et al. 2008).

Differentiating bipolarity in children with ADHD is vital given that bipolar adolescents with a history of stimulant exposure prior to the onset of BD might have an earlier age at onset of BD than those without prior stimulant exposure. Because the coexistence of ADHD and mania seriously complicates the course and treatment of children, understanding the compatibility of these disorders has important clinical implications in the management of this population (Scheffer et al. 2005). A history of ADHD was associated with a significantly diminished acute response to both divalproex sodium and lithium as a primary treatment for the manic phase of BD (Biederman et al. 1998). We have unfortunately no studies in Turkey that systematically evaluates short-term or long-term treatment or functioning of pediatric bipolar patients.

## Conclusions

The diagnostic characteristics of mania in children and adolescents in Turkey has been controversial. Despite ongoing controversy, the view that pediatric BD is rare or non-existent has been increasingly challenged not only by case reports but also by systematic research. In accordance with the current literature, euphoric mood and episodic course is rare in Turkish children and adolescents and the affective phenomenology is often mixed and dysphoric with affective storms and temper outbursts, while psychotic features are seen during adolescence. Comorbidity (especially with ADHD) is a big issue in accurate diagnosis and treatment. We need more studies that systematically evaluates pharmacotherapy and psychotherapy responses in youth with BPD so as to

better understand factors affecting treatment response and long term outcome. We believe multicenter international studies are likely to play very important role in our understanding of bipolarity in childhood.

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The authors have no financial relationships or conflicts to disclose.

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