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Symptom Dimensions and Trajectories of Functioning Among Bipolar Youth: A Cluster Analysis

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Abstract

Background—Accurate assessment of pediatric bipolar disorder is important for allocating appropriate treatment, but it is complicated by significant heterogeneity in symptom presentation and high rates of comorbidity. Investigating clinical subtypes of the disorder may help to clarify diagnostic boundaries and inform targeted treatment. This study used a full diagnostic instrument to examine symptom patterns among youth with bipolar disorder.

Method—Trained interviewers completed the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) with 71 children (7 to 13 years of age) and families as part of the baseline assessment for a randomized clinical trial of Child- and Family-focused Cognitive-Behavioral Therapy (CFF-CBT) compared with treatment as usual for pediatric bipolar disorder. All participants met DSM-IV-TR criteria for a bipolar spectrum disorder. Hierarchical and K-means cluster analyses were performed. Resultant clusters were compared on symptom severity and psychosocial functioning at baseline and across treatment.

Results—Two distinct symptom profiles emerged: “dysregulated/defiant” and “classic presentation.” The dysregulated/defiant cluster was characterized by more externalizing and disruptive behaviors, whereas the classic cluster presented with more severe depression, hallmark

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manic symptoms, anxiety, and inattention. CFF-CBT consistently promoted psychosocial coping skills, such as problem solving and self-control, for the dysregulated/defiant cluster. Treatment as usual also promoted these skills among the individuals in the classic presentation group but not those with symptoms in the dysregulated/defiant cluster.

Discussion—Pediatric bipolar disorder may be characterized by distinct phenotypes with unique etiologies and pathways to impairment. The use of a parametric approach to classify the diverse symptom presentations helped yield valuable insights into how to promote the best prognosis for improved functional outcomes in CFF-CBT versus treatment as usual for youth with pediatric bipolar disorder.

Keywords

pediatric bipolar disorder; functioning; cognitive-behavioral therapy; symptom dimensions

Children with pediatric bipolar disorder (BD) experience a wide variety of symptoms and functional impairments that can interfere with both accurate diagnosis and effective treatment. The diagnostic picture of pediatric BD is complicated by high rates of co-occurring disorders. As many as 75% of youth with elevated manic symptoms meet criteria for another psychiatric disorder.¹ The most common comorbid conditions include attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and anxiety disorders, estimates of which are as high as 62%, 53%, and 69%, respectively.^{2–4} Such high rates of comorbidity may be explained by overlapping symptom criteria. In addition, the symptoms observed in pediatric BD may reflect dysfunction in neurocircuitry responsible for modulating emotion and cognition that cut across multiple diagnostic categories, thus yielding behavioral symptom profiles that overlap with other disorders,⁵ such as the new diagnosis of disruptive mood dysregulation disorder (DMDD)^{6,7} in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).⁸

A few studies have used data reduction techniques to assess for common patterns in the heterogeneous symptom presentations. Primarily, existing studies have used factor analyses to identify linear combinations of variables (latent variables), and their results vary widely. In a 2007 publication, Papolos et al⁹ derived 10 independent factors from the Child Bipolar Questionnaire,¹⁰ whereas, in a 2002 study, Youngstrom et al¹¹ derived only a single mania factor using the Young Mania Rating Scale (YMRS).¹² In a 2008 analysis of teacher report measures of mania, Youngstrom et al¹³ again found a 1 factor resolution for the YMRS, although they found a 3-factor resolution for the Child Mania Rating Scale.¹⁴ In a 2007 study, Frazier et al¹⁵ derived unifactorial structures for the YMRS, K-SADS Mania Rating Scale,¹⁶ and Children's Depression Rating Scale (CDRS)¹⁷; however the CDRS shifted to a 2-factor structure when assessed in adolescents.

This heterogeneity could be explained by age differences in the youth who were surveyed and developmental variations in manic symptom presentations.¹⁸ However, the few studies that have looked at age differences in pediatric mania factor resolutions have found relatively minimal variation across age groups.^{15,18} Another source of these discrepancies may be the nature of the assessment tools used to identify and define symptoms of bipolar disorder; specifically, all of these studies have relied on brief screening tools rather than formal

diagnostic assessments. Given the significant comorbidity in pediatric BD, it is possible that clinically meaningful diagnostic subtypes of pediatric BD involve a variety of psychiatric symptoms, rather than just mood dysregulation. Under this scenario, a cluster analysis, which aims to group “like” subjects on the basis of key defining variables, may help yield valuable insight into important subgroups of patients with specific constellations of illness features. Indeed, among adults with BD, cluster analyses have identified specific subtypes of mania, such as a more classic subtype, psychotic mania, depressive mania, and highly recurrent mania.¹⁹ To our knowledge, no previous studies have assessed symptom clusters in pediatric BD using the full range of Axis I psychiatric symptoms.

The identification of patterns of symptom variability, including the range of mood and other potential comorbid symptoms, may help establish more tailored treatment programs that better match planned interventions to patient symptoms and characteristics at baseline. As the field moves towards a more dimensional and domain-based understanding of clinical “disorders” with the National Institute of Mental Health’s Research Domain Criteria (RDoC) initiative,²⁰ identifying how symptoms and functional impairments cluster within individuals in systematic ways may help clarify important biological, psychological, or social processes that “hang together” and relate to potential treatment targets and mechanisms for change and recovery. Thus, the purpose of the current study was to analyze symptom level criteria across all diagnostic categories from a structured clinical diagnostic interview to determine whether meaningful clusters of mood disorder symptoms and symptoms of other disorders emerged in youth with pediatric BD. In addition, given the poor long-term psychosocial prognosis associated with pediatric BD, a secondary objective was to assess whether identified subgroups correspond to differences in psychosocial functioning and response to psychosocial treatment.

METHODS

Participants

Participants were children and young adolescents ($N=71$) recruited from a specialty mood disorders clinic in an academic medical center in a large Midwestern urban area. All participants were part of a randomized clinical trial of a family-based psychosocial treatment for pediatric BD. Youth meeting DSM-IV-TR²¹ criteria for a bipolar spectrum disorder (bipolar disorder I, II, or not otherwise specified) who were between 7 and 13 years of age were eligible to enroll. Participants were permitted to take psychiatric medication provided they had been on a stable dosage for a minimum of 4 weeks before their baseline assessment. This criterion was intended to exclude enrollment of children who needed acute stabilization via a higher level of care (ie, hospitalization) before being able to participate in psychotherapy. Participants were excluded from the study if the child scored <70 on the Kaufman Brief Intelligence Test, Second Edition,²² was actively psychotic, acutely suicidal requiring imminent intervention, reported active substance use, or suffered from any serious neurological or other medical condition. Participants were also excluded if their primary caretaker was reporting severe symptoms of mania (>6 point cutoff score on the Altman Self Mania Rating Scale²³) or depression (>28 on the Beck Depression Inventory²⁴); as these

scores may indicate the need for individual treatment of the parent's mood disorder before the parent would be able to participate in family-based therapy.

Procedures

After obtaining informed consent, youth with suspected or diagnosed bipolar spectrum disorder and their parents were screened for eligibility for the study. The child and parent(s) were interviewed separately by trained interviewers using the Washington University Kiddie Schedule of Affective Disorders and Schizophrenia (WASH-U-KSADS)^{25,26} After confirmation of a bipolar spectrum disorder diagnosis and the administration of inclusion/exclusion measures, youth and parents completed a battery of baseline assessments and questionnaires, including measures of symptoms and psychosocial functioning, before randomization and initiation of psychosocial treatment.

Psychosocial Treatment

Details regarding assignment to and length and content of treatment have been previously described.^{27,28} In brief, all eligible participants were randomly assigned to either Child- and Family-Focused Cognitive Behavior Therapy (CFF-CBT) or the control condition, psychosocial treatment as usual (TAU). CFF-CBT integrates CBT with psychoeducation and complementary mindfulness-based and interpersonal/family therapy techniques tailored to address the range of therapeutic needs in families affected by pediatric BD. Table 1 provides details concerning the participants and content in the treatment sessions. Treatment was delivered by pre- and post-doctoral clinicians trained by the developers on the CFF-CBT manual in a mood disorders clinic. Participants randomized to TAU were assigned a therapist (clinical psychology doctoral student, postdoctoral fellow, psychiatry fellow, or social work intern) in the General Psychiatry Clinic who received 1 hour of training on pediatric BD; psychotherapy in TAU was otherwise unstructured. Both treatment groups received 12 weekly sessions.

Measures

Diagnosis and symptom assessment was conducted by trained interviewers using the WASH-U-KSADS.²⁵ The WASH-U-KSADS is a semi-structured clinician-administered interview designed to yield a DSM-IV²⁹ diagnosis; parents and children are interviewed separately. The measure includes expanded mania and depression sections with items developed specifically to assess prepubertal mood symptoms, patterns of ultrarapid and ultradian cycling, both lifetime and current episodes, the specific timing of onsets and offsets for all symptoms and syndromes, and symptoms of ADHD and all other major DSM-IV psychiatric diagnoses. This diagnostic instrument has demonstrated good test-retest reliability and inter-rater reliability.²⁶ For the analysis in this study, item ratings for each current symptom on a Likert-scale were used as input for the cluster analysis.

Child psychosocial functioning—*Global Functioning* was assessed using the Children's Global Assessment Scales (CGAS) and the Clinical Global Impressions-Bipolar Version (CGI-BP). The CGAS^{30,31} is a clinician-report measure that assesses the severity of impairment in functioning across multiple domains including family, social, school, and work. Scores range from 1 to 100, with lower scores indicating lower functioning. The CGI-

BP³² is a modified version of the Clinical Global Impressions scale designed specifically for individuals with bipolar disorder. The clinician rates the global severity of the child's symptoms for the dimensions of mania, depression, attention deficit/hyperactivity, psychosis, and aggression, as well as overall illness, on a Likert scale ranging from 1 (not at all ill) to 7 (most extremely ill).

Youth coping was assessed using the Youth Coping Index (YCI),³³ a 31-item self-report measure that captures 3 types of coping strategies: personal development, positive reappraisal and problem solving, and stress management/communication.

Social skills were measured using the Social Skills Rating System (SSRS).³⁴ The SSRS is a nationally standardized measure of overall social competence with parent and child report versions. Both versions of the measure include subscales in cooperation, assertion, and self-control. In addition, the youth report yields an empathy subscale and the parent version yields subscales of responsibility, externalizing, internalizing, and hyperactive behaviors.

Quality of life was measured with the Questionnaire for Measuring Health-Related Quality of Life in Children (KINDL).³⁵ The 24-item, parent report measure is designed to capture six different aspects of quality of life: physical, emotional, self-esteem, family, friends, and school. Items are rated on a 5-point Likert scale and summed within and across subscales for a total score.

Family Functioning was assessed using the Family Adaptability and Cohesion Evaluation Scale (FACES).³⁶ This 30-item parent-report instrument measures attitudes about the family and interpersonal relationships within the family unit. Parents report on their perceptions of the family's dynamics. Responses are assessed on 5-point Likert scale.

Data Analytic Approach

To identify subsets of patients with similar symptom profiles, we conducted an agglomerative hierarchical cluster analysis using SPSS v20.0. Preliminary inspection of the WASH-U-KSADS data revealed a number of symptoms that were excluded from our analysis because they were not endorsed by any participants in the sample or because the highest endorsement by any participant in the sample was not clinically significant (ie, rated "doubtful"). Pearson's bivariate correlations for the remaining symptom level criteria indicated strong and significant associations ($r \geq 0.5$, $P < 0.05$) between 5 combinations of variables: (1) depressed mood and depressed appearance ($r = 0.59$; $P < 0.001$); (2) negative self image and tearfulness ($r = 0.52$; $P < 0.001$); (3) depressed mood and anhedonia ($r = 0.55$; $P < 0.001$); (4) depressed mood and fatigue ($r = 0.54$, $P < 0.001$); (5) flight of ideas and pressured speech ($r = 0.63$, $P < 0.001$). To reduce the shared variance among these pairs of variables, depressed appearance, tearfulness, anhedonia, fatigue, and pressured speech were excluded from the cluster analysis.

The cluster analysis was performed with the remaining WASH-U-KSADS symptoms using Ward's method of minimum variance with a squared Euclidean distance measure. Ward's method is distinct from other methods because it uses an analysis of variance approach to evaluate the distances between clusters. The best distinguished cluster solution was

determined from inspection of the dendrogram [Note to production: Insert call out for supplementary digital content **here**]. K-means clustering was used to determine the content of the distinct symptom profiles. Resultant clusters were then used as a grouping variable to compare means of symptom level criteria across the groups (via analysis of variance). Significance was set at $P < 0.05$ for these comparisons.

We conducted exploratory analyses on whether clusters moderated treatment trajectories on measures of functioning over time using mixed-effects regression models (MRMs). MRMs are well suited for the analysis of longitudinal data; they are robust to the data dependency that occurs with the repeated assessments of individuals over time and are efficient in handling missing data.³⁷ Separate MRMs were evaluated for each functioning outcome measure and included effects for cluster, treatment (CFF-CBT [coded 0], TAU), time (baseline, week 4, week 8, week 12, and 6 months), and the cluster $\times$ treatment $\times$ time interaction to examine moderation; models also included all associated lower order interactions. Because this study was not initially stratified or powered based on cluster groups, our moderator analysis followed the methods outlined by Kraemer and Kupfer,³⁸ who recommend that effect sizes define exploratory moderators of treatment because of the potential for the statistical significance of the moderator to change with sample size. Consistent with recommended conventions (eg, Kraemer 2008,³⁹ Pincus et al 2011,⁴⁰ Vitiello et al 2012⁴¹), our exploratory analyses of the moderating effects of cluster used a less stringent α threshold of 0.10. Moderators meeting this threshold were then explored with respect to the magnitude of the treatment effects at each level of the proposed moderators.³⁸

RESULTS

Number of Clusters

Agglomeration coefficients generated by a cluster analysis revealed that a 2-cluster solution best distinguished the cases. The two resultant clusters were labeled according to their most distinguishing characteristics; a “classic presentation” cluster ($n = 28$) and a “dysregulated/defiant” cluster ($n = 43$). Demographic and clinical characteristics for the 71 participants are summarized in Table 2. Significant differences in WASH-U-KSADS symptoms defining the 2 clusters are presented in Table 3.

Cluster Characteristics

Depressive symptoms—The classic presentation cluster demonstrated particularly severe symptoms of depression relative to the dysregulated/defiant cluster (see Table 3 for statistical contrasts). Specifically, the classic presentation cluster demonstrated more severe symptoms of depressed mood, social withdrawal, social isolation, lack of appetite, psychomotor agitation, psychomotor retardation, inability to think, guilt, low self-esteem, hopelessness, suicidal ideation, and rejection sensitivity. Both groups demonstrated similar symptoms of temporal quality of depressed mood, irritability, insomnia/hypersomnia, increased appetite, somatic symptoms, reactivity of depressed mood, diurnal variation, and leaden paralysis.

Manic and psychotic symptoms—The classic presentation cluster was characterized by more severe hallmark symptoms of mania relative to the dysregulated/defiant cluster (Table 3), including elevated mood, increased energy, increased productivity, flight of ideas, distractibility, uninhibited people seeking, and sharpened thinking. Both groups demonstrated similar symptom severity of expansive mood, grandiosity, decreased need for sleep, increase in goal directed activity, hyperactivity, judgment (ability to make safe decisions and choices), hypersexuality, hallucinations, and delusions.

Anxiety and eating disorder symptoms—The only observed differences indicated that the classic presentation cluster was characterized by more separation anxiety and generalized anxiety (Table 3). The 2 clusters demonstrated similar levels of panic attacks, agoraphobia, specific phobia, social phobia, obsessive thoughts, compulsive behaviors, hypochondriasis, enuresis, nightmares, binge eating behaviors, body image disturbance, and fear of weight gain.

Disruptive Behavior Symptoms—The dysregulated/defiant cluster reported more severe symptoms of temper outbursts, arguing with adults, actively defying rules/requests, blaming others for mistakes, being easily annoyed, and spiteful/vindictive behavior (Table 3). The classic presentation reported elevated symptoms of inattentiveness, hyperactivity, and impulsivity (Table 3). Consistent with this, 100% of the classic cluster met criteria for comorbid ADHD. The 2 clusters demonstrated similar levels of deliberately annoying others, anger/resentfulness, destruction of property, aggression, and deceitfulness.

Did the Clusters Differ on Measures of Functioning at Baseline?

When compared on measures of functioning at baseline (Table 4), the classic presentation cluster had more severe ratings on the CGI-BP Scale overall, ADHD, and depression ratings. They also demonstrated more difficulties with assertive and internalizing behaviors, poorer quality of peer relationships and lower school adjustment/performance. The dysregulated/defiant cluster was characterized by poorer family cohesion and communication.

Did the Clusters Interact with Treatment Group to Predict Change in Functioning Across Treatment?

Our exploratory analyses examined whether the two clusters differed in treatment outcomes in CFF-CBT versus TAU. The clusters did not moderate change in depressive or manic symptoms. There were two main findings regarding functional outcomes. First, a Cluster x Treatment x Time interaction was found for frequency of the self-reported coping skill, positive reappraisal/problem solving, $b=2.44$, $SE=1.20$, $P=0.05$, corresponding to a medium effect size ($d=0.46$; Figure 1). Neither treatment increased use of positive reappraisal/problem solving in the classic presentation, whereas, in the group who received CFF-CBT, these skills significantly increased in the dysregulated/defiant cluster over time.

The second finding was a marginal Cluster x Treatment x Time interaction predicting the self-reported social skill, self-control, $b=1.07$, $SE=.59$, $P=0.07$, also corresponding to a medium effect size ($d=0.43$, Figure 2). In the group who received TAU, the classic presentation cluster improved, whereas the dysregulated/defiant cluster decreased, in self-

control over time. In the group who received CFF-CBT, both the classic presentation and the dysregulated/defiant clusters improved over time in self-control.

The clusters did not moderate change in global functioning (as assessed by the CGAS and CGI-BP) or quality of life (as measured by the KINDL and FACES).

DISCUSSION

Pediatric BD during childhood shares many similarities with other disorders such as ODD, ADHD, and DMDD. Failure to adequately discriminate or classify these pathologies may lead to inadequate diagnosis and treatment, which can gravely impact prognosis into adulthood.⁴² Because comorbidity tends to be the norm in pediatric BD, identifying and managing combinations of conditions in the context of pediatric BD is an important clinical and research target.⁴³ A better understanding of how typical constellations or patterns of symptoms in pediatric BD dictate the course of functioning and response to different treatment options may ultimately lead to better prognosis for youth with bipolar disorder.^{44,45} To our knowledge, this is the first study to explore how specific patterns of symptoms impact the daily functioning of bipolar youth and differentially affect trajectories of functioning over the course of psychosocial treatment. These findings are clinically relevant to the treatment of pediatric bipolar disorder, as a more thorough assessment of symptom heterogeneity could help to better match treatment to patients. Our cluster analysis revealed two distinct clusters of symptoms among bipolar youth. The classic presentation cluster was characterized by notably more severe depressive symptoms than the dysregulated/defiant cluster on 7 of 9 DSM-IV²⁹ symptom criteria for a major depressive episode. The classic presentation was also characterized by more severe hallmark symptoms of mania, accompanied by prominent symptoms of anxiety and problems with attention/hyperactivity. This presentation is consistent with the adult course of bipolar disorder that is dominated by depressive episodes and internalizing symptoms.⁴⁶ In contrast, the dysregulated/defiant cluster was characterized by more symptoms of disruptive behaviors. It is important to note that the clusters did not differ in the proportion of youth with a BP-NOS diagnosis, indicating that the dysregulated/defiant cluster is not simply comprised of children with subthreshold symptoms. Furthermore, both groups experienced clinically significant episodes of mania and depression, so the dysregulated/defiant cluster can also be distinguished from a profile of chronic irritability (eg, as in DMDD⁴⁷) and the “broad” phenotype.⁴⁸ Thus, these clinical phenotypic distinctions are not well captured by current diagnostic categories.

These patterns of symptoms were associated with unique impairments in the daily functioning of these youth. The classic presentation demonstrated more problems with assertiveness, poorer quality of relationships with peers, and difficulties with school adjustment and performance. These impairments are clinically intuitive; a child who is prominently withdrawn, depressed, and anxious is likely to have difficulty speaking openly and appropriately, approaching peers or initiating social interactions, and finding motivation to complete schoolwork; such a child might also feel anxious or overwhelmed about attending school. Treatment targeting deficits in social skills, behavioral activation, and executive functioning may be critical in ameliorating long-term social impairment⁴⁹ and

academic underperformance or absenteeism⁵⁰ for these children. The dysregulated/defiant cluster was characterized by poorer family cohesion and communication. Externalizing behaviors in pediatric BD may represent a distinct pathway to dysfunction within the family unit. Although it is somewhat surprising that these externalizing behaviors did not have an impact on social functioning, peers may perceive children who act out or engage in risky behavior as more popular, whereas externalizing problems are more distressing to parents. Equally, a dysfunctional family unit may lead to fewer consistent boundaries in parenting, and in turn, result in more externalizing behaviors among children. Regardless of etiology, it may be particularly important to teach parents of these youth skills to promote more adaptive communication strategies within the whole family and how to better respond to their child's disruptive behaviors. Our earlier work indicates that, indeed, improving family cohesion is a key ingredient of family based treatment for pediatric BD.⁵¹

Regarding treatment outcomes, CFF-CBT uniquely increased positive reappraisal and problem solving among individuals in the dysregulated/defiant cluster. These symptoms fluctuated but they did not show meaningful change in either cluster among those who received TAU. CFF-CBT is specifically designed to help the child and family deal with, react to, and problem solve the outbursts and episodes of rage that are characteristically seen in pediatric BD, but that are less common in more prevalent psychiatric disorders such as unipolar depression or anxiety.⁵² Because these impairing outbursts are disproportionately prevalent in pediatric BD compared with other pediatric psychiatric disorders,⁵³ the CFF-CBT manual devotes significant time and effort to promoting strategies to ameliorate their consequences. Surprisingly, use of positive reappraisal and problem solving decreased in those who received CFF-CBT in the classic presentation cluster. It is possible that this subset of youth with severe depressive symptoms is in need of different kinds of coping skills (eg, behavioral activation, positive self-scripts, assertiveness training) than those with rage episodes. For example, the classic presentation group who received CFF-CBT did improve in self-control, indicating that feeling more empowered and in control of their emotions and behaviors may be more helpful for children who tend to be withdrawn or lack assertiveness. Collectively, these findings suggest that clinically, dysregulated/defiant children may be in greater need of a treatment approach that teaches them to react to and problem solve rage episodes whereas youth with a predominantly depressed and anxious presentation may benefit from more traditional CBT for depression approaches that increase activity and self-esteem.

We also found that the individuals in the dysregulated/defiant cluster who received CFF-CBT improved in self-control. TAU also promoted self-control skills among the classic presentation group, but not among the children in the dysregulated/defiant cluster. The overall improvements in self-control in children who received CFF-CBT are expected as affect regulation is a central ingredient of CFF-CBT.⁵⁴ This skill is repeatedly reinforced throughout treatment through behavioral management, recognition of emotional states and triggers, and development of coping strategies to manage negative emotional reactivity. In contrast, the less structured and specialized treatment in TAU was less effective at yielding these improvements for children with more externalizing behavior. This finding highlights the importance of managing emotional reactivity and impulsivity in youth with bipolar disorder, especially among individuals with significant externalizing symptoms.

Strengths and Limitations

This study had several strengths, including the use of a novel data analytic approach to detect symptom patterns across a diverse set of symptoms and leveraging a randomized, controlled trial of family-based psychotherapy to predict outcomes. Limitations included that randomization to treatment was not stratified by cluster, and multiple comparisons were undertaken in the analysis; thus the trial was not originally designed with the power to detect these moderation patterns. Our analyses should be considered exploratory, and they warrant replication. Furthermore, our sample was representative of only 1 clinical setting and therefore results may not generalize to other settings. Given the young age range and early onset that characterized this sample, our cluster analysis could not include symptom ratings for past episodes, which may be an important consideration for patients with a history of multiple distinct episodes.⁵⁵ In addition, differential dropout in the acute phase of TAU versus CFF-CBT^{27,28} may have influenced treatment outcomes. Finally, although these analyses provide a step toward matching treatments to patient characteristics, we did not examine causal pathways. The examination of treatment mediators must be explored in future research to identify not only what treatments work for whom, but to better elucidate “why” treatments work for certain subsets of patients.

CONCLUSIONS

The exploratory findings presented here have possible implications for the assessment of pediatric BD and subsequent treatment decision-making. This study raises the possibility that simply meeting diagnostic threshold for pediatric BD may not be sufficient for determining what psychosocial treatment works best for which children and their families. Notably, using a parametric approach to classify the diverse symptom presentations in pediatric BD helped yield initial insights as to how to promote the best prognosis for improved functional outcomes in CFF-CBT versus TAU. Careful consideration should be given to the presence of comorbid conditions and a child’s specific pattern of symptoms, which may, in turn, enhance treatment response. This preliminary study points to distinct phenotypes of pediatric BD with unique functional prognoses. Accordingly, future research should address potential etiological pathways, or intermediate phenotypes, that explain these symptom profiles among youth with bipolar disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cluster by Treatment by Time Interaction Predicting Positive Reappraisal and Problem Solving (YCI)

Figure 2.
Cluster by Treatment by Time Interaction Predicting Self Control (SSRS)

Session participants and content for Child- and Family-Focused Cognitive Behavior Therapy for Pediatric Bipolar Disorder

Table 1

Session	Participants	Topics Covered
1	Child and parents together	<ul style="list-style-type: none"> • Orientation to treatment/goal-setting • Engagement and relationship-building
2	Child and parents together	<ul style="list-style-type: none"> • Psychoeducation about pediatric bipolar disorder • Mood charting
3	Parents only	<ul style="list-style-type: none"> • Affect regulation • Establishing routines; identifying difficult feelings; anger management
4	Child only	<ul style="list-style-type: none"> • Affect regulation skills • Labeling emotions; recognizing difficult feelings; triggers
5	Child only	<ul style="list-style-type: none"> • Coping skills • Problem-solving; positive thinking
6	Parents only	<ul style="list-style-type: none"> • Positive thinking; mantras; reframing negative thoughts; mindfulness
7	Child only	<ul style="list-style-type: none"> • Communication skills and interpersonal problem-solving
8	Parents only	<ul style="list-style-type: none"> • Promoting social competence; behavior management; balanced life
9	Parents, child, siblings together	<ul style="list-style-type: none"> • Family coping and problem-solving
10	Child and parents together	<ul style="list-style-type: none"> • Social support
11	Child and parents together	<ul style="list-style-type: none"> • Reflection on RAINBOW[*] experience and review
12	Child and parents together	<ul style="list-style-type: none"> • Celebration; follow-up plan

* RAINBOW stands for
Routine

Affect Regulation

I can do it

No negative thoughts & live in the Now

Be a good friend & Balanced lifestyle for parents
Oh, how can we solve this problem?
Ways to get support

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Table 2

Demographic and Clinical Characteristics of 71 Children with Pediatric Bipolar Disorder

	Classic Presentation (n = 28)				Dysregulated/Defiant (n = 43)				Overall (n = 71)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age	9.70	1.42	9.68	1.72			9.69	1.60		
	N	%	N	%	N	%	N	%		
Sex (female)	8	29	21	49			29	41		
Race										
<i>White</i>	16	57	22	51			38	54		
<i>Black</i>	8	29	13	30			21	30		
<i>Hispanic</i>	1	4	6	14			7	10		
<i>American Indian or Alaskan Native</i>	2	7	1	2			3	4		
<i>Native American or Pacific Islander</i>	1	4	0	0			1	1		
Income (<\$50,000)	9	38	15	42			24	40		
Diagnosis										
Bipolar I	8	29	15	35			22	32		
Bipolar II	3	11	1	3			4	6		
Bipolar NOS	17	61	27	63			42	62		
Comorbid conditions										
Anxiety disorder	9	32	15	38			24	36		
ADHD **	28	100	26	65			54	79		
ODD	9	32	16	41			25	37		
CD *	5	18	1	3			6	9		
Family History of Bipolar Disorder^A	16	59	8	44			24	53		

ADHD indicates attention deficit hyperactivity disorder; CD, conduct disorder; NOS, not otherwise specified; ODD, oppositional defiant disorder

When data points were missing, percentages were calculated based on the total number of valid cases for which data were available

Especially limited data were available for the variable family history of bipolar disorder (Classic n = 27/28; Dysregulated/Defiant n = 18/43; Overall n = 45/71)

100.0 > P **
'50.0 > P *
*

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Table 3

Significant Differences Between Clusters on WASH-U-KSADS Symptoms*

Symptom**	Classic N= 28		Dysregulated/Defiant N = 43		t	P
Depression	Mean	SD	Mean	SD		
Depressed mood ^a	4.11	1.29	3.02	1.32	-3.42	0.001
Social withdrawal ^a	2.86	1.51	2.14	1.28	-2.15	0.001
Social isolation ^a	2.29	1.30	1.65	1.04	-2.27	0.026
Lack of appetite ^a	2.14	1.15	1.33	0.75	-3.64	0.001
Psychomotor agitation ^a	3.36	1.25	2.28	1.33	-3.41	0.001
Psychomotor retardation ^a	2.50	1.35	1.63	1.09	-2.99	0.004
Inability to think ^a	4.32	0.94	2.58	1.22	-6.39	<0.001
Guilt ^a	3.50	1.32	1.79	0.97	-6.31	<0.001
Low self-esteem ^a	4.21	1.34	3.30	1.37	-2.76	0.007
Hopelessness ^a	2.46	1.40	1.72	1.14	-2.45	0.017
Suicidal ideation ^a	2.96	1.73	2.14	1.44	-2.21	0.033
Rejection sensitivity ^a	2.89	1.47	1.72	1.08	-3.87	<0.001
Mania/Psychosis						
Elevated mood ^a	3.79	1.17	3.51	1.33	-2.58	0.012
Increased energy ^a	4.32	1.09	3.37	1.56	-2.80	0.007
Increased productivity ^a	2.57	1.17	1.63	0.95	-3.73	<0.001
Flight of ideas ^a	3.86	1.51	2.58	1.42	-3.61	0.001
Distractibility ^a	3.54	0.51	2.91	0.97	-3.15	0.002
Uninhibited people seeking ^a	2.46	1.04	1.67	1.02	-3.18	0.002
Sharpened thinking ^a	2.61	1.07	1.91	1.19	-2.52	0.014
Anxiety						

Symptom ^{**}	Classic N= 28	Dysregulated/Defiant N = 43	t	P		
Depression	Mean	SD	Mean	SD		
Separation anxiety ^a	2.61	1.23	1.56	0.96	-4.03	<0.001
Generalized anxiety ^a	2.21	0.92	1.53	0.83	-3.24	0.002
Disruptive Behaviors						
Temper outbursts ^b	2.29	0.66	2.84	0.48	4.06	<0.001
Arguing with adults ^b	1.71	0.98	2.40	0.76	3.30	0.002
Defying rules/requests ^b	1.71	1.18	2.37	0.85	2.73	0.008
Blaming others ^b	1.71	0.98	2.47	0.70	3.77	<0.001
Easily annoyed ^b	2.00	1.02	2.53	0.77	2.52	0.014
Spiteful/vindictive ^b	1.07	0.72	1.98	0.94	4.34	<0.001
Attention Deficit/Hyperactivity						
Inattention ^a	8.11	1.42	5.35	2.42	-5.44	<.001
Hyperactivity ^a	4.46	1.53	2.65	1.91	-4.21	<.001
Impulsivity ^a	2.29	0.98	1.70	1.17	-2.21	0.030

* A number of symptoms were excluded from the cluster analysis because they were not endorsed by any participants in the sample or because the highest endorsement by any participant in the sample was not clinically significant (ie, rated "doubtful"); all symptoms of posttraumatic stress disorder; all symptoms of substance, alcohol, or nicotine use disorders; rule breaking and delinquency symptoms of conduct disorder; amnesia; fugue; dissociative identity disorder; depersonalization; derealization; visual hallucinations; delusions; incoherence; derailing; illogical thinking; neologisms; alusia; Tourette syndrome; motor/vocal tics; transient tic disorder; encopresis; sleep terror; and sleep walking. In addition, because strong and significant associations ($r \geq 0.5$, $P < 0.05$) were found for 5 combinations of symptom variables (depressed mood and depressed appearance, negative self image and tearfulness, depressed mood and anhedonia, depressed mood and fatigue, and flight of ideas and pressured speech), depressed appearance, tearfulness, anhedonia, fatigue, and pressured speech were excluded from the cluster analysis to reduce the shared variance among these pairs of variables.

**

All contrasts were computed with 69 degrees of freedom

^a Classic Presentation > Dysregulated/Defiant

^b Classic Presentation < Dysregulated/Defiant

Table 4

Comparison of Clusters on Measures of Psychosocial Functioning at Baseline

	Classic <i>N</i> = 28		Dysregulated/Defiant <i>N</i> = 43	
	Mean	SD	Mean	SD
CGAS^a	49.00	6.25	50.02	5.21
CGI-BP^a				
Overall psychiatric disorder *	4.31	0.62	4.00	0.55
ADHD **	3.89	0.85	2.95	1.13
Mania/Mixed	3.52	0.80	3.62	0.73
Depression *	3.48	0.98	3.00	1.02
Aggression	3.37	1.01	3.60	0.73
Psychosis	1.54	1.14	1.42	0.88
Youth Coping Inventory Total^b	98.06	17.47	94.98	17.00
Positive appraisal/problem solving	31.46	7.17	30.24	8.20
Spiritual/personal	38.14	10.21	36.81	10.78
Communication/tension management	20.20	7.11	20.42	4.95
Social Skills Rating System^b				
Cooperation	13.48	2.89	14.00	3.92
Assertion *	13.07	2.30	14.52	3.04
Empathy	15.15	3.79	15.59	2.97
Self-control	10.77	3.06	11.92	3.67
Social Skills Rating System^c				
Cooperation	7.84	3.58	8.19	3.02
Assertion	11.91	3.76	11.62	3.11
Responsibility	11.06	3.75	9.99	2.74
Self-control	8.04	3.49	7.56	2.68
Externalizing	8.08	2.25	8.59	2.19
Internalizing *	8.12	2.28	6.52	2.40
Hyperactivity	9.20	1.89	8.49	2.06
KINDL^c	57.65	13.89	61.01	8.99
Physical well being	69.91	19.23	69.77	17.41
Emotional well being	65.51	21.61	72.82	15.06
Family	58.56	23.07	52.62	18.71
Friends *	48.30	19.60	58.43	19.81
School *	55.25	19.49	65.31	15.31
Self esteem	48.15	21.00	47.24	14.39

	Classic <i>N</i> = 28		Dysregulated/Defiant <i>N</i> = 43	
	Mean	SD	Mean	SD
FACES^c				
Cohesion [*]	29.96	3.43	27.38	4.93
Flexibility	27.15	3.03	24.88	5.57
Disengaged	13.12	3.27	15.12	5.31
Enmeshed	13.38	3.32	13.55	3.99
Rigid	20.63	4.07	20.64	3.98
Chaotic	14.27	5.55	15.43	5.15
Family satisfaction	33.62	8.31	31.05	8.77
Family communication [*]	38.46	6.07	34.79	7.11

^{*} $P < 0.05$,

^{**} $P < 0.01$

^a Clinician-rated measure;

^b Child-reported measure;

^c Parent-reported measure

CGAS indicates Children's Global Assessment Scales; CGI-BP, Clinical Global Impressions-Bipolar Version; FACES, Family Adaptability and Cohesion Evaluation Scale; KINDL, Questionnaire for Measuring Health-Related Quality of Life in Children