Co-morbid Disruptive Behavior Disorder and Aggression Predict Functional Outcomes and Differential Response to Risperidone Versus Divalproex in Pharmacotherapy for Pediatric Bipolar Disorder

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Abstract

Objective: Co-morbid diagnoses, such as disruptive behavior disorders (DBDs) and high levels of aggression, are extremely common among youth with pediatric bipolar disorder (PBD) and may interfere with treatment response; however, they have rarely been examined as predictors of response to pharmacotherapy. The current study examines co-morbid DBD and aggression prospectively as predictors of pharmacotherapy outcome, as well as potential moderators of response to a specific medication (risperidone vs. divalproex), among children with PBD.

Methods: Data are from a prospective 6-week double-blind, placebo-controlled, randomized outpatient medication treatment trial of risperidone versus divalproex for manic episodes in 65 children 8–18 with PBD. Outcome measures were administered at pretest, post-test, and weekly during the 6 weeks of treatment. Mixed-effects regression models were used to examine pharmacotherapy response.

Results: Results indicated that youth with co-morbid DBD experienced greater improvement in manic symptoms in response to risperidone versus divalproex, whereas youth with non-co-morbid DBD experienced similar trajectories of symptom improvement in both medication groups. In addition, the non-DBD group experienced greater improvement in global functioning over time as compared with youth with co-morbid-DBD, and this gap increased over the course of treatment. Results also indicated that high-aggression youth experienced worse global functioning by end treatment versus low-aggression youth.

Conclusions: In conclusion, a co-morbid diagnosis of DBD and/or high levels of aggressive symptoms in youth with PBD may be important clinical predictors of variation in treatment response to pharmacotherapy. These findings may help researchers and clinicians develop tailored treatment approaches that optimize symptom and functional outcomes.

Introduction

UNDERSTANDING THE PREDICTORS of pharmacotherapy response in pediatric bipolar disorder (PBD) is integral to developing more personalized and effective interventions. Youth with PBD frequently present with a heterogeneous clinical picture, including co-morbid diagnoses and considerable levels of aggression, which can camouflage the primary diagnosis and complicate treatment. The objective of this study is to examine how salient clinical factors, including co-morbid disruptive behavior disorders (DBDs) and high levels of aggressive features, may influence response to pharmacotherapy in PBD.

PBD is a refractory and debilitating illness associated with high levels of variability in treatment response. Specifically, findings indicate that >40% of PBD youth have a poor response to pharmacotherapy, with low rates of remission and high rates of recurrence (Emslie et al. 2003; Geller et al. 2008; Birmaher et al. 2009).

In recent years, research has increasingly focused on understanding the factors that may predict outcome to pharmacotherapy among youth with PBD to enhance treatment outcomes. Findings, albeit mixed, suggest that clinical features such as symptom severity and co-morbid diagnoses may predict treatment nonresponse (Masi et al. 2004).

Co-morbid diagnoses are extremely common among youth with PBD (Emslie et al. 2003) and may interfere with treatment response, particularly a co-morbid DBD (oppositional defiant disorder [ODD], conduct disorder (CD) or DBD-NOS (not otherwise specified [NOS] or attention-deficit/hyperactivity disorder [ADHD])). For example, Strober et al. (1998) found that co-morbid psychiatric disorders, including ADHD, were associated with nonresponse to lithium, whereas a study conducted by Kafantaris et al. (1998) found that co-morbid ADHD, among other diagnoses, did not interfere with lithium response. Scheffer et al. (2005) demonstrated that the use of adjunctive mixed amphetamine salts in addition to

divalproex was more effective than divalproex alone in treating patients with PBD and co-morbid ADHD and that divalproex alone was not an effective treatment. In a recent naturalistic study, Masi et al. (2004) demonstrated that co-morbid externalizing disorders were predictive of poorer outcomes and treatment nonresponse among children and adolescents, as measured by the clinician-rated Clinical Global Impressions-Improvement for Bipolar Disorders Scale.

Aggressive behavior (whether or not it is associated with co-morbid DBD) is a key feature in many PBD cases, and is often the primary reason that parents seek treatment (MacMillian et al. 2006). Thus, the reduction of irritability, explosive rage episodes, and violence toward family and peers are often key targets for pharmacological intervention. Despite this fact, very few studies have specifically examined aggressive behavior as an outcome or predictor of response in pharmacotherapy studies for PBD. Macmillian et al. (2006) examined aggressive behavior as an outcome in a retrospective chart review study of divalproex versus oxcarbazepine in youth with bipolar disorder and found that divalproex was more effective than oxcarbazepine in reducing aggressive symptoms. A study by Barzman et al. (2006) demonstrated that adolescents with cooccurring bipolar disorder and DBD demonstrated similar positive outcomes on impulsivity and reactive aggression with quetiapine and divalproex. Similarly, an open trial (Barzman et al. 2005) found that divalproex effectively treated severe aggression and irritability in youth with PBD in an inpatient setting. Although not specific to PBD, research examining youth with chronic aggressive behavior has shown that divalproex is an efficacious treatment for aggression in placebo-controlled studies (Donovan et al. 2000; Blader et al. 2009). We acknowledge that all of these studies examine aggression as an outcome variable (rather than a predictor) in pharmacotherapy response studies; however, to our knowledge, no study to date has examined aggressive behavior as a predictor of pharmacotherapy response in youth with PBD.

Increased understanding of how clinical features, such as co-morbid diagnoses and aggression, may affect traditional pharmacologic interventions can facilitate treatment planning, including the selection of medications as well as the need for adjunctive interventions (e.g., psychosocial treatment, use of additional medications). To this end, the current study expands on previous work by specifically examining co-morbid DBD and aggression prospectively as predictors of treatment outcome, as well as potential moderators of response to a specific medication (risperidone vs. divalproex) among children and adolescents with PBD. We hypothesized that the presence of co-morbid DBD would be associated with poorer symptom improvement and functional outcomes as compared with youth with PBD without co-morbid DBD diagnoses. We also hypothesized that the presence of higher levels of aggression at baseline would be associated with poorer symptom improvement and functional outcomes as compared with youth with lower levels of aggression. Exploratory hypotheses examined interactions between co-morbidity, aggression, and medication type (risperidone vs. divalproex).

Methods

Design overview

Data for this study were collected as part of a prospective 6-week double-blind randomized outpatient medication treatment trial of risperidone and placebo (resembling a divalproex capsule) versus divalproex and placebo (resembling a risperidone tablet) for manic

episodes in children with PBD (Pavuluri et al. 2010). This study was approved by the University of Illinois at Chicago Institutional Review Board.

Sample

Participants in this study were recruited from our Pediatric Mood Disorders Program, an outpatient subspecialty clinic at a major urban academic medical center. Participants were screened to determine whether they qualified for the study according to inclusion and exclusion criteria. Inclusion criteria were as follows: a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) diagnosis of bipolar I disorder (mixed or manic episode) as determined via diagnostic interview administered to the patient and family (see below); age 8–18 years; and medication free or clinically unstable on medication. Parents of participants consented for their children to be washed out of their current medications at study entry. Potential participants were excluded if they demonstrated active substance use measured by a urine drug screen, had serious medical problems, had a history of allergy to risperidone or divalproex, or if they had autism or nonaffective psychotic disorders.

One-hundred and eight potential subjects were initially screened to obtain a sample of 66 participants who were randomized to treatment conditions. Forty-two potential participants did not meet the study criteria due to a history of worsening on one of the two study medications ($n = 14$), a diagnosis of bipolar II disorder ($n = 5$) or bipolar disorder not otherwise specified ($n = 15$), use of cannabis ($n = 4$), seizure history ($n = 2$), and inability to comply with the scheduled visits required for the protocol ($n = 2$). Sixty-five participants received at least 1 week of treatment, and 43 completed 6 weeks (further details regarding the study procedures can be found in Pavuluri et al. 2010). The mean age of the participants was 10.85 years (standard deviation [SD] = 3.34), and 40 (60.6%) were male. The ethnic composition of the sample was 71% Caucasian, 17% African-American, and 2% Hispanic. Thirty-five percent had a mixed episode at baseline, and 65% had a manic episode at baseline. Fifty-two (79%) had rapid cycling, 29 (44%) had a co-morbid DBD (62% of which was ADHD), and 5 (8%) had co-morbid anxiety disorders. Of note, and pertinent to data analyses, the co-morbid DBD group and the aggression group were relatively distinct in this sample. The co-morbid DBD subgroup was primarily comprised of youth with an ADHD diagnosis (or in a few cases, multiple co-morbidities such as diagnoses of ADHD and ODD, or ADHD and an anxiety diagnosis) and demonstrated little overlap with the high-aggression subgroup.

Study medications

The study medications were administered in a double-blind, double-dummy randomized manner by our investigational pharmacist. Investigational staff involved in rating efficacy and safety measures, parents, caregivers and subjects were blind to the medication received. Risperidone was initiated at 0.25 mg to 0.50 mg per day. The dose was titrated to a maximum of 2 mg per day by increments of 0.25–0.5 mg every 2 days to achieve a maximum tolerable level by day 7. For tolerability purposes, a maximum dose of 2 mg per day was used; a review of outcomes from various clinical trials involving risperidone in children and adolescents with PBD suggested that there was no added advantage of using higher risperidone doses than 2.0–2.5 mg/day (Bishop and Pavuluri 2008). Divalproex was titrated up to 15 mg/kg/day over 3 days, and

serum level was measured at the end of 5 days. No dose adjustments were permitted after the first week.

Measures

All patients underwent a standard diagnostic evaluation to screen for inclusion in the study and to collect baseline measures. Each child and the parent or legal guardian were interviewed using the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al. 1994), and episodes were defined by using the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). All diagnostic interviews, including the administration of the WASH-U-KSADS and the episode assessment portion of the K-SADS-PL, were completed by trained physicians or other doctoral-level clinicians. High inter-rater reliability was established (Cohen's kappa = 0.94).

Presence of co-morbid DBD (i.e., ADHD, ODD, and/or conduct disorder) was assessed at baseline by using the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al. 1994). Diagnosis of a co-morbid DBD was made with reference to symptoms during the euthymic phase.

Aggression was assessed at baseline via the Overt Aggression Scale-Aggression Subscale (Yudofsky 1986). The OAS is a standardized behavioral checklist that rates the frequency of episodes occurring during the past week in four main categories, representing escalating violent behavior (verbal aggression; physical aggression against objects; physical aggression against self; and physical aggression against others) (Yudofsky 1986). Youth aggression scores ranged from 2 to 40 ($M = 15.0$, $SD = 8.53$) and were normally distributed in the current sample, with skewness = 0.82 (standard error [SE] = 0.31) and kurtosis = 0.01 (SE = 0.61). For this study, a mean split was used to categorize youth with low versus high aggressive features; a mean split was preferred over a median split given that the sample mean was closer to the midpoint of the OAS and, thus, better classified youth with low- versus high-aggression scores.

Outcome measures were administered at pretest, post-test, and weekly during the 6 weeks of treatment to examine both the magnitude and trajectory of symptom change over time. Three scales were used to assess PBD symptoms and global functioning across treatment.

Manic symptoms were assessed via the Young Mania Rating Scale (YMRS) (Young et al. 1978). The YMRS is a clinician-rated measure of symptoms during a manic state. The YMRS consists of 11 items, each with explicitly defined levels of severity (0–4 or 0–8). The scale is designed to be administered by a trained clinician during a 15 to 20 minute interview. Severity ratings are based on the patient's subjective experience during the past 48 hours and the clinician's observations during the interview. Inter-rater reliability is 0.93, and concurrent validity with other mania rating scales is 0.77 to 0.89. This instrument has been validated for use with children (Youngstrom et al. 2002).

Depressive symptoms were assessed by using the Child Depression Rating Scale-Revised (CDRS-R) (Poznanski et al. 1984). The CDRS-R is a reliable and valid clinician-rated instrument for measuring the severity of depression in children. Scores are calculated by summing scores across the 17 items that assess depressive symptoms, each of which are rated on a five-point Likert-type scale.

Global functioning was assessed via the Child and Adolescent Functioning Assessment Scale (CAFAS) (Hodges and Wong

1997). The CAFAS is a clinician-administered rating scale designed for youth aged 7–17. Impairment is operationalized as the degree to which the youth's problems interfere with his or her functioning in various life roles (e.g., student, family member, worker, friend, citizen; Bates 2001). Test-retest reliability coefficients have been generally positive [0.74–0.76 (Bird et al. 1987); 0.69–0.95 (Shaffer et al. 1983)].

Analytic approach

Mixed-effects regression models (MRMs) (Laird and Ware 1982) were conducted via SPSS MIXED to examine youth response to treatment. All statistics presented in this study were derived from intent-to-treat analyses, such that data from all randomized subjects with at least one assessment after baseline ($N = 65$) were analyzed (Fisher et al. 1990). The mixed-effects models accounted for each participant's outcome data at each time point (pretest and weekly throughout 6 weeks of treatment). The MRMs are well suited for the analysis of longitudinal data; these models are robust to the data dependency that occurs with the repeated assessments of individuals over time and can also handle missing data. Further, rather than focusing solely on categories of response versus nonresponse, these models allowed us to examine how treatment response trajectories may vary in important ways among the predictors. We used random intercept and trend modeling, a subclass of MRMs that accounts for each individual's distinct initial level of symptom severity/functioning and rate of change over time.

Separate models were conducted for each predictor variable (Co-morbidity, Aggression) on each outcome measure (manic symptoms-YMRS, depressive symptoms-CDRS-R, and global functioning-CAFAS). The clinical predictors were dichotomously coded to reflect (a) the absence or presence (0, 1) of a co-morbid DBD diagnosis and (b) low versus high levels (0, 1) of baseline aggression. Each model included the intercept, time, medication type (0 = divalproex), clinical predictor, and the Clinical Predictor $\times$ Time interaction to examine differences in treatment response trajectories for youth as a function of predictor group (i.e., low vs. high aggression; absence vs. presence of co-morbidity). In addition, Clinical Predictor $\times$ Time $\times$ Medication Type (divalproex, risperidone) effects were included in each model to examine differential medication responses among the clinical predictors; thus, all possible two-way interactions (Medication Type $\times$ Time, Clinical predictor $\times$ Medication type) were also included in the model as controls. Last, a quadratic term for time and all higher order interactions with the quadratic term were included as controls to account for nonlinear treatment responses. For ease of presentation, we report only models that relate directly to our stated hypotheses in the Results section next.

Results

Dosing of risperidone and divalproex sodium

The mean dose for risperidone at endpoint was 1.44 mg/day ($SD = 0.72$). The mean dose for divalproex sodium at endpoint was 838.24 mg/day ($SD = 260.58$). Serum level at endpoint was 96.1 $\mu\text{g/mL}$. Medication dose for the clinical predictor groups is included in Table 1.

Preliminary analyses

We report the demographic and clinical characteristics, as well as descriptive statistics for all study measures at baseline and end treatment, for the total sample and stratified by the aggression and

TABLE 1. DEMOGRAPHIC CHARACTERISTICS, CLINICAL CHARACTERISTICS, AND DESCRIPTIVE STATISTICS FOR ALL STUDY MEASURES FOR THE TOTAL SAMPLE AND BY CLINICAL PREDICTOR SUBGROUP

	Total <i>M</i> (<i>SD</i>) or <i>n</i> (%) <i>n</i> =65	Co-morbid DBD <i>M</i> (<i>SD</i>) or <i>n</i> (%) <i>Yes</i> (<i>n</i> =29)	No (<i>n</i> =36)	Aggression <i>M</i> (<i>SD</i>) or <i>n</i> (%) <i>High</i> (<i>n</i> =21)	Low (<i>n</i> =39)
Age (years)	10.85 (3.34)	10.14 (3.30)	11.52 (3.29)	9.74 (3.56)	11.11 (3.17)
Gender: male	40 (61%)	20 (69%)	19 (53%)	16 (76%)	20 (51%)*
Ethnicity: White	37 (57%)	20 (69%)	17 (48%)	10 (48%)	25 (64%)
Med.: Divalproex	33 (50.8)	17 (59%)	16 (44%)	10 (48%)	21 (54%)
Med.: Risperidone	32 (49.2)	12 (41%)	20 (56%)	11 (52%)	18 (46%)
Divalproex dose (mg/day)	803.57 (300.00)	796.05 (303.94)	809.78 (303.55)	812.50 (262.20)	790.00 (330.17)
Risperidone dose (mg/day)	1.35 (0.67)	1.37 (0.69)	1.34 (0.66)	1.47 (0.72)	1.25 (0.63)
Co-morbid DBD	29 (45%)	29 (100%)	0 (0%)*	10 (47.6%)	16 (41%)
Co-morbid anxiety	5 (8%)	1 (3%)	4 (11%)	1 (5%)	4 (11%)
Baseline OAS	15.00 (8.53)	16.42 (9.33)	13.91 (7.84)	24.86 (5.84)	9.69 (3.53)*
Baseline YMRS	28.72 (7.05)	29.44 (7.24)	28.12 (6.95)	30.90 (7.39)	27.59 (6.79)
Baseline CDRS=R	41.38 (15.63)	39.96 (12.78)	42.50 (17.69)	44.52 (17.69)	39.85 (14.57)
Baseline CAFAS	57.70 (49.21)	67.41 (57.02)	50.00 (41.27)	100.48 (50.84)	36.15 (29.79)*
Endpoint OAS	2.98 (3.76)	2.80 (4.10)	3.14 (3.51)	2.80 (4.23)	2.96 (3.71)
Endpoint YMRS	8.17 (8.70)	8.30 (8.15)	8.05 (9.39)	8.73 (10.66)	7.74 (7.94)
Endpoint CDRS=R	26.40 (9.93)	25.85 (10.57)	26.91 (9.54)	23.67 (9.83)	27.63 (9.81)
Endpoint CAFAS	17.01 (35.79)	21.67 (36.31)	12.35 (35.27)	25.33 (43.73)	11.00 (27.70)

Medication dosage refers to endpoint values.

**t*-tests comparing groups = $p < 0.05$.

DBD=disruptive behavior disorder; OAS=Overt Aggression Scale; YMRS=Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale, Revised; CAFAS=Child and Adolescent Functional Assessment Scale; SD=standard deviation; Med.=medication type.

DBD co-morbidity subgroups in Table 1. Chi square and *t*-test analyses were conducted to examine group differences in the demographic and clinical characteristics between the medication groups as well as the clinical predictor groups, as indicated in Table 1 and reported next.

The risperidone ($n=32$) and divalproex groups ($n=33$) were compared and were not significantly different in gender, racial background, co-morbidity with a DBD, age, or aggression. The two groups were significantly different from each other in terms of treatment completion ($\chi^2=3.8$, $p<0.05$), with fewer youth completing treatment in the divalproex group ($n=17$, 51.5%) as compared with the risperidone group ($n=27$, 84.4%). Reasons for premature discontinuation (Pavuluri et al. 2010) such as increased irritability, hospitalization, being lost to follow-up, ineffectiveness, depression, suicidal behavior, rash, and tics did not differ significantly among the predictor groups as discussed next.

As just noted, we report the age, gender, ethnicity, medication assignment and endpoint dose values, co-morbidities, aggression levels, and descriptive statistics for all outcome measures for youth with and without DBD co-morbidity ($n=29$ and $n=36$, respectively) in Table 1. Analyses revealed that the DBD co-morbidity groups were not significantly different with regard to age, gender, racial background, and attrition. Further, groups did not significantly differ in terms of their baseline level of aggression or medication condition. Differences in the outcome measures among groups are discussed in the longitudinal analyses presented next.

Additionally, Table 1 presents sample characteristics and descriptive statistics for the aggression subgroups. Youth with high levels of baseline aggression ($n=21$) versus low baseline aggression ($n=39$) were compared and were not significantly different with regard to age, racial background, and attrition. Further, the groups did not differ in terms of their co-morbidity with a DBD or medication condition. However, the two groups were significantly different from each other in terms of gender ($\chi^2=6.4$, $p<0.05$).

Given this difference, *post hoc* analyses were examined while controlling for gender. Of note, 5 youth did not provide baseline aggression data and, thus, were excluded from all analyses examining aggression as a predictor. Chi-square and *t*-test analyses confirmed that youth with and without aggression data did not significantly differ in terms of gender, racial background, attrition, medication condition, or co-morbidity with DBD. Differences in outcome measures for high and low-aggression youth across treatment are discussed next.

Finally, preliminary analyses examined the relationship between the clinical predictors, aggression, and DBD co-morbidity in this sample. Findings demonstrated that aggression was equally distributed across co-morbid and non-co-morbid youth and, similarly, rates of DBD co-morbidity were equally distributed across high- and low-aggression groups. In our sample, aggression and DBD co-morbidity were not significantly correlated, $r_{PB}=0.15$, $p=ns$. Thus, findings indicate that aggression and DBD co-morbidity are distinct, nonoverlapping constructs within the current sample.

DBD co-morbidity and treatment response

We hypothesized that the presence of co-morbid DBD would be associated with poorer treatment response as compared with PBD youth without co-morbid DBD diagnoses. In addition, exploratory hypotheses examined interactions between co-morbidity and medication type (risperidone vs. divalproex). To test these hypotheses, MRMs as just specified were conducted separately for manic symptoms, depressive symptoms, and global functioning. Results of the three models, including parameter estimates, SEs, *t*-values, and *p*-values, are presented in Table 2; baseline and endpoint values for manic symptoms, depressive symptoms, and global functioning are reported in Table 1.

The first model examined co-morbid DBD as a predictor of manic symptom response. As shown in Table 2, results for the Time

TABLE 2. CO-MORBID DISRUPTIVE BEHAVIOR DISORDER MIXED-EFFECTS REGRESSION MODELS ON MANIC SYMPTOMS (YOUNG MANIA RATING SCALE [YMRS]), DEPRESSION SYMPTOMS (CHILD DEPRESSION RATING SCALE-REVISED [CDRS=R]), AND GLOBAL FUNCTIONING (CHILD AND ADOLESCENT FUNCTIONING ASSESSMENT SCALE [CAFAS])

Effect	Manic symptoms (YMRS)				Depression symptoms (CDRS=R)				Global functioning (CAFAS)			
	Estimate	SE	t (df)	p	Estimate	SE	t (df)	p	Estimate	SE	t (df)	p
Intercept	28.19	1.78	15.82 (93)	0.00	45.88	3.01	15.22 (79)	0.00	52.48	9.56	5.49 (68)	0.00
Time	-7.85	1.16	-6.75 (290)	0.00	-6.64	1.56	-4.25 (291)	0.00	-11.94	3.83	-3.12 (255)	0.00
Medication type	-1.89	2.73	-0.69 (93)	0.49	-6.54	4.54	-1.44 (81)	0.15	-5.91	14.40	-0.41 (69)	0.68
Co-morbid DBD	4.94	2.91	1.70 (95)	0.09	-11.6	4.92	-2.36 (80)	0.02	16.98	15.62	1.09 (68)	0.28
DBD×Time	-4.79	1.88	-2.55 (295)	0.01	0.92	2.53	0.37 (293)	0.72	-11.72	6.16	-1.90 (257)	0.05
DBD×Medication×Time	7.21	2.78	2.59 (302)	0.01	-3.74	3.72	-1.01 (299)	0.32	15.01	9.02	1.67 (272)	0.10

Each model included additional control variables, including a quadratic term for time and all possible two-way interactions among the variables; only theoretically relevant effects are reported above. SE = standard error; df = degrees of freedom; DBD = disruptive behavior disorders.

effect indicated that all youth experienced an improvement in symptoms across treatment. In addition, in support of our hypothesis, findings revealed a significant Comorbid DBD×Time interaction, indicating that manic symptom response over time differed for youth with co-morbid DBD versus non-DBD youth. However, in contrast to the direction of our hypotheses, examination of manic symptom trajectories suggests that youth with co-morbid DBD experienced a slightly steeper (i.e., stronger) treatment response initially (e.g., from baseline to week 2, mean YMRS scores improved by 15.31 points for youth with DBD versus a 12-point reduction in YMRS scores for youth with non-DBD co-morbidities), although the magnitude of group differences diminished by mid-treatment (e.g., week 3 mean YMRS scores for youth with DBD were 11.19 (SD=7.13) and 10.39 (SD=8.84) for youth with non-DBD co-morbidities). However, this interaction was qualified by the significant three-way Co-morbidity×Medication Type×Time interaction, indicating that treatment response over time for co-morbid versus non-co-morbid youth was moderated by medication type. To best illustrate this interaction, Figure 1 displays mean YMRS scores across treatment as a function of co-morbidity status and medication type. As the figure reveals, youth with PBD with co-morbid DBD experienced greater improvement in manic symptoms in response to risperidone versus divalproex, whereas youth with non-co-morbid DBD experienced similar trajectories of symptom improvement in both medication groups. Moreover, youth with PBD with co-morbid DBD in the risperidone group evidenced the strongest symptom response overall, although all groups showed similar responses by end treatment.

Results for depressive symptoms indicated a significant main effect for time, such that all youth experienced an improvement in symptoms across treatment. Results also indicated a significant main effect for co-morbidity, with youth with co-morbid-DBD experiencing lower levels of depressive symptoms overall ($M=30.58$, $SD=13.01$) as compared with youth with non-DBD co-morbidities ($M=33.35$, $SD=14.55$). However, in contrast to hypotheses, youth with and without co-morbid DBD experienced

FIG. 1. Mean manic symptoms (YMRS) scores over time as a function of disruptive behavior disorders (DBD) co-morbidity and medication type. DBD=presence of a co-morbid disruptive behavior disorder; No DBD=absence of a co-morbid disruptive behavior disorder; D=divalproex; R=risperidone; YMRS=Young Mania Rating Scale. *Differences at each time point $p < 0.05$.

similar trajectories of depressive symptom improvement over time (i.e., nonsignificant effect for Co-morbidity $\times$ Time; see Table 1 for endpoint CDRS values by DBD group). Thus, co-morbidity was not associated with a poorer treatment response for depressive symptoms. Further, co-morbidity did not significantly moderate the trajectories of symptom response among the two medication groups.

Regarding global functioning, results of the third model revealed that again, all youth improved in terms of their global functioning (as measured by the CAFAS) across treatment. In addition, findings revealed a trend for the Co-morbid DBD $\times$ Time interaction, which indicated that improvement in global functioning across treatment differed for the co-morbid-DBD versus non-co-morbid youth. Findings held across medication type, as indicated by the nonsignificant Co-morbidity $\times$ Time $\times$ Medication. To illustrate this trend, Figure 2 displays mean CAFAS scores over time as a function of co-morbidity. Consistent with our hypotheses, results indicate that the non-DBD group experienced a differential pattern of change in global functioning over time as compared with youth with co-morbid-DBD. Further, as the figure reveals, group differences became more exaggerated across treatment: the co-morbid group's initial steep reduction in functional problems appeared to plateau by mid-treatment, whereas the non-DBD group experienced consistent declines in problematic functioning across treatment. By end treatment, mean global functioning for co-morbid youth ($M=21.67$, $SD=36.31$) continued to exceed clinical significance, signaling the need for continued outpatient care, whereas mean scores for non-co-morbid youth approached nonimpaired functioning ($M=12.35$, $SD=35.27$).

Aggressive features and treatment response

We also hypothesized that aggressive features may complicate treatment for youth with PBD, as indicated by a poorer treatment response for youth with high levels of baseline aggression versus youth with low levels of aggression. To examine the influences of aggression on each outcome measure, we conducted three MRMs identical to the models just described. Results of these models are

FIG. 2. Mean global functioning (CAFAS) scores over time as a function of DBD co-morbidity. CAFAS=Child and Adolescent Functioning Assessment Scale, DBD=disruptive behavior disorders.

presented in Table 3, and Table 1 lists the baseline and endpoint values for manic symptoms, depressive symptoms, and global functioning for high- and low-aggression youth.

Results for manic symptom response revealed a significant main effect for time, such that all youth improved in their manic symptoms across treatment. However, in contrast with expectations, youth with high baseline aggression demonstrated similar manic symptom responses as low-aggression youth (i.e., nonsignificant effects for Aggression $\times$ Time; see Table 1 for endpoint YMRS values). Further, the three-way interaction of Aggression $\times$ Time $\times$ Medication was not significant, indicating that high- and low-aggression youth experienced similar improvement across medication type. Similarly, findings for depressive symptoms revealed that all youth improved in response to pharmacologic intervention. Response trajectories for depressive symptoms were similar for high- versus low-aggression youth, across medication groups. As Table 1 indicates, all youth experienced similar levels of depressive symptoms by end-point treatment. Thus, aggression did not predict manic or depressive symptom response to pharmacotherapy.

Regarding global functioning, findings revealed a significant main effect for aggression as well as a significant Aggression $\times$ Time interaction. That is, global functioning trajectories differed for high- versus low-aggression youth with PBD in response to treatment. Figure 3 displays mean global functioning (CAFAS) scores across treatment for the low- and high-aggression groups. As the figure reveals, all youth improve in terms of global functioning across treatment. However, in line with expectations, high-aggression youth experienced worse global functioning by end treatment versus low-aggression youth. Specifically, low-aggression youth experienced functioning within the normal range ($M=11.00$, $SD=27.70$), whereas high-aggression youth continued to experience clinically significant levels of impairment ($M=25.33$, $SD=43.73$). Again, findings held across medication type, as evidenced by the nonsignificant Aggression $\times$ Time $\times$ Medication. Thus, despite similar symptom response trajectories, high-aggression youth experienced attenuated improvement in global functioning as compared with their low aggression counterparts.

Post hoc analyses

Given the gender differences in aggression, *post hoc* analyses included gender as a control in all MRMs for aggression as well as DBD co-morbidity. Results revealed similar effects to those obtained in the original models, such that the inclusion of gender did not alter the significance, direction, or magnitude of findings in any model.

Discussion

This study examined co-morbid DBD and aggression as predictors of pharmacological treatment response in a randomized controlled trial of divalproex versus risperidone for PBD. Youth with PBD present with heterogeneous symptom profiles, which may complicate diagnosis and decision-making regarding treatment. The examination of important clinical features that distinguish youth within the broader diagnostic group of PBD could inform treatment planning. In this study, we expected youth whose symptom profiles were characterized by co-morbid DBD or higher levels of aggression to demonstrate poorer response to treatment. We also conducted exploratory analyses to examine whether patients with co-morbid DBD or higher aggression responded differently to divalproex versus risperidone.

TABLE 3. AGGRESSIVE FEATURES MIXED-EFFECTS REGRESSION MODELS ON MANIC SYMPTOMS (YOUNG MANIA RATING SCALE [YMRS]), DEPRESSION SYMPTOMS (CHILD DEPRESSION RATING SCALE-REVISED [CDRS=R]), AND GLOBAL FUNCTIONING (CHILD AND ADOLESCENT FUNCTIONING ASSESSMENT SCALE [CAFAS])

Effect	Manic symptoms (YMRS)			Depression symptoms (CDRS=R)			Global functioning (CAFAS)					
	Estimate	SE	t (df)	p	Estimate	SE	t (df)	p	Estimate	SE	t (df)	p
Intercept	27.86	1.85	15.05 (83)	0.00	39.09	3.33	11.73 (69)	0.00	34.55	7.93	4.36 (67)	.00
Time	-9.04	1.21	-7.46 (268)	0.00	-4.98	1.61	-3.09 (274)	0.00	-9.95	3.84	-2.59 (253)	0.01
Medication Type	-3.50	2.54	-1.38 (85)	0.17	0.03	4.56	0.01 (70)	0.99	2.04	10.84	0.19 (67)	0.85
Aggression	5.87	3.00	1.96 (83)	0.05	6.78	5.41	1.26 (69)	0.21	74.42	12.86	5.70 (66)	0.00
Aggression × Time	-2.14	1.94	-1.11 (267)	0.27	-3.49	2.59	-1.35 (273)	0.18	-20.43	6.15	-3.32 (252)	0.00
Aggression × Med × Time	1.99	2.94	0.68 (278)	0.50	6.28	3.89	1.62 (279)	0.11	7.84	9.24	0.85 (265)	0.40

Each model included additional control variables, including a quadratic term for time and all possible two-way interactions among the variables; only theoretically relevant effects are reported above.

Youth in this sample demonstrated a decrease in mania symptoms over the course of treatment. However, contrary to our hypotheses, youth with co-morbid DBD did not uniformly demonstrate poorer outcomes than youth without co-morbid DBD. In fact, overall, youth with co-morbid DBD showed a stronger treatment response initially, although the gap between the two groups was diminished by post-treatment. Interestingly, the association between co-morbidity and treatment outcomes was moderated by medication type. Youth with PBD with co-morbid DBD experienced greater reduction in manic symptoms in response to risperidone versus divalproex, whereas non-co-morbid youth experienced similar trajectories in both medication groups. DBD co-morbidity was not associated with a poorer treatment response in depressive symptoms and did not relate to differential response by medication group. In terms of global functioning, consistent with our hypothesis, youth with co-morbid DBD demonstrated worse outcomes overall compared with the non-co-morbid DBD group. These results indicate that youth with PBD with co-morbid DBD may experience greater improvements in mania symptoms and global functioning in response to risperidone compared with divalproex, whereas youth with PBD without co-morbid DBD may benefit equally from either medication. In addition, youth with co-morbid DBD may exhibit more significant global functional impairment that is not adequately addressed by either of these medications and may warrant further intervention through psychosocial treatment or other methods.

Level of aggressive symptoms at baseline was not associated with treatment outcome in manic symptoms. Youth with higher levels of aggressive symptoms showed comparable improvement in mania symptoms to youth with low levels of symptoms, and this did not differ by medication group. Response in depressive symptoms showed a similar pattern. In terms of global functioning, however, level of aggression at baseline appeared to predict outcome. All youth improved in global functioning as a result of treatment, but higher-aggression youth exhibited worse functional outcomes compared with lower-aggression youth. This finding was consistent across both medication groups. These results indicate that, although

FIG. 3. Mean global functioning (CAFAS) scores over time as a function of baseline aggression level (high, low). *Differences at each time point $p < 0.05$. CAFAS=Child and Adolescent Functioning Assessment Scale.

level of aggression at baseline may not directly relate to symptom outcomes as a result of pharmacological treatment, youth with high levels of aggression are significantly more impaired functionally than their peers with lower levels of aggression and that pharmacological treatment does not necessarily close this gap. Again, this finding speaks to the potential need for adjunctive treatment, psychosocial or otherwise, and more extensive assessment of global functioning in addition to symptoms, to further address the increased functional impairment in youth with PBD who demonstrate high levels of aggressive behavior.

Conclusions

A co-morbid diagnosis of DBD and/or high levels of aggressive symptoms in youth with PBD may be important clinical predictors of variation in treatment response to pharmacotherapy. In particular, youth with co-morbid DBD may demonstrate a greater response to risperidone in terms of both reductions in mania symptoms and improved global functioning. Further, although pharmacotherapy treatment with divalproex or risperidone resulted in improved symptoms and functional outcomes across youth with a range of aggressive behavior, youth with PBD who demonstrate higher levels of aggression at baseline may show attenuated response compared with their low-aggression peers in terms of global functioning post-treatment. In light of the relatively poor response to pharmacotherapy treatment overall in youth with PBD (Emslie et al. 2003), these findings indicate the importance of examining the heterogeneous profiles of youth with PBD presenting for pharmacological treatment and studying how youth with diverse clinical profiles may respond in different ways to treatment. A more nuanced understanding of how the complex constellation of PBD symptoms may affect response to various pharmacological treatment regimens may improve our ability to develop individualized treatment approaches, and ultimately improve rates of response to pharmacotherapy.

Strengths of this study include the examination of a novel and significant research question (i.e., whether these common clinical features of youth with PBD predicted response to pharmacological treatment), the use of a prospective randomized controlled design, blinded clinician ratings, and an MRM approach to data analyses. However, findings should be cautiously interpreted in light of the limitations of this study design, most notably a relatively small sample size, lack of multiple informants on outcome measures, and limitations in the specificity of the YMRS in assessing child mania symptoms. It is possible that the significant medication by co-morbidity interaction may be influenced, in part, by the non-specificity of the YMRS measure. In addition, although co-morbid DBD and aggression were considered separate constructs for the purposes of this study, and this distinction was supported by our data, the differentiation of co-morbid DBD symptoms and aggression relative to a bipolar disorder presentation, which often encompasses both aggression and disruptive behavior within the context of manic and depressive episodes, is complicated and warrants further in-depth study. Nevertheless, this study represents an important initial investigation of how certain clinical predictors in youth with PBD may relate to pharmacological treatment response and inform more tailored treatment approaches, an important area for future study.

Clinical Significance

PBD is a chronic and debilitating disorder, the symptoms of which demonstrate variable and discouraging responses to our

current pharmacological treatments. Youth with PBD present to treatment with heterogeneous clinical pictures; however, there have been very few studies that have examined how different clinical features of the disorder may be associated with treatment response. In this study, we demonstrated that youth with PBD with co-morbid DBD or high levels of aggression may show consistent variability in treatment response compared with youth with PBD with no DBD co-morbidity or youth with lower levels of aggressions. Results, though preliminary, suggest that risperidone may yield greater improvements in mania symptoms for youth with co-morbid DBD compared with divalproex. In addition, findings from this study suggest that youth with co-morbid DBD and higher levels of aggression may continue to demonstrate greater impairment in global functioning after pharmacotherapy and that adjunctive psychosocial interventions aimed at improving global functioning may be particularly indicated for these subgroups of youth with PBD. Future studies, including those with larger samples and more comprehensive measurement plans, will further aid researchers and clinicians in identifying important clinical predictors of treatment outcome in PBD and developing associated tailored treatment approaches that optimize symptom and functional outcomes.

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Disclosures

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All other authors declare that they have no conflicts of interest.

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