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Conversion from bipolar disorder not otherwise specified (BP-NOS) to bipolar I or II in youth with family history as a predictor of conversion

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Abstract

Background—Bipolar disorder-not otherwise specified (BD-NOS) is an imprecise, heterogeneous diagnosis that is unstable in youth. This study reports rates of conversion from BD-NOS to BD-I or II in children aged 8–12, and investigates the impact of family history of bipolar disorder and depression on conversion.

Methods—As part of the Multi-Family Psychoeducational Psychotherapy (MF-PEP) study, 27 children (6–12 years of age) diagnosed with BD-NOS at baseline were reassessed every 6 months over an 18-month period. Family history of bipolar disorder and depression was assessed at baseline.

Results—One-third of the sample converted from BD-NOS to BD-I or II over 18-months. Having a first-degree relative with symptoms of bipolar disorder and having a loaded pedigree for diagnosis of depression each were associated with conversion from BD-NOS to BD-I or II (odds ratio range: 1.09–3.14; relative risk range: 1.06–2.34).

Limitations—This study had very low power (range: 10–45) given the small sample size, precluding statistical significance of non-parametric Fisher's Exact test findings.

Conclusions—This study replicates the previous finding of a high rate of conversion from BD-NOS to BD-I or II among youth, and suggests conversion is related to symptoms of bipolar disorder or depression diagnoses in the family history. Additional research is warranted in a larger sample with a longer follow-up period.

Keywords

Bipolar disorder; Child; Adolescent; Diagnostic conversion; Family history

1. Introduction

Bipolar disorder-not otherwise specified (BD-NOS) is commonly diagnosed in youth with a bipolar spectrum disorder (BPSD) when hypomanic or manic episodes fall short of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) duration criteria. DSM-IV defines BD-NOS as “Disorders with bipolar

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Conflict of interest

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features that do not meet criteria for any specific bipolar disorder” and include presentations such as rapid mood alteration for days without meeting threshold severity or duration for a specific bipolar disorder, recurrent hypomania without depressive symptoms, and hypomanic episodes with depressive symptoms too infrequent for diagnosis of cyclothymia (American Psychiatric Association, 2000). However, children with BD-NOS experience a similar degree of impairment as children with bipolar I (BD-I) or bipolar II disorder (BD-II) (Axelson et al., 2006). BD-NOS is an unstable diagnosis. In recent studies, 29% of youth converted from BD-NOS to BD-I or BD-II over a two-year period (Birmaher et al., 2006), and 38% converted over four-years (Birmaher et al., 2009). At two-year follow-up of the Course and Outcome of Bipolar Youth (COBY) study (Birmaher et al., 2006; Birmaher et al., 2009), female sex and long duration of illness were associated with higher rates of conversion; no predictors were reported at four-year follow-up.

BPSDs are clearly heritable (Rudolph et al., 2006). Family history of BD and/or depression is a risk for BPSD (Akiskal et al., 1979; Hodgins et al., 2002; Todd et al., 1993; Gershon et al., 1975). Youth with BD-NOS (Bader and Dunner, 2007) and “sub-threshold BD” (Lewinsohn et al., 2000) have elevated family histories of BD, similar to youth with BD-I and BD-II. However, the role of family history in conversion is not clear.

Previous studies have compared subtypes of BD based on presence of a first- and/or second-degree relative (Birmaher et al., 2009; Bader and Dunner, 2007), but have not explored the significance of “loaded” and “multigenerational” family histories. Akiskal and colleagues (Akiskal et al., 1983) define a “loaded pedigree” as containing three or more first- or second-degree relatives of the proband who have the same disorder. A “multigenerational pedigree” refers to three consecutive generations affected by the same disorder. These classifications have had predictive power in family history studies of mood disorders (Akiskal et al., 1979; Akiskal et al., 1983) despite the fact that BD has only emerged in the public consciousness relatively recently, thus, underreporting of three-generation pedigrees is likely.

When assessing family history, distinguishing diagnostic- and symptom-level illness appears important. Gershon and colleagues (Gershon et al., 1982) found that MDD diagnosis, but not symptoms of depression, predicted outcome. On the other hand, given the historical under-recognition of BD, it is possible that symptoms, but not disorders might be reported for those who truly have BD.

1.1. Purpose of this study

This study investigated: (1) the rate of conversion from BD-NOS to BD-I or II over 18 months in 27 children; and (2) the role of family history of BD and depression in predicting conversion. The following hypotheses were tested: (1) 20% of children diagnosed with BD-NOS will convert to BD-I or BD-II over 18 months; (2) Conversion rates will be higher for children with: (a) one or more first-degree relatives with a history of manic symptoms or BD; (b) a loaded pedigree of manic symptoms, BD or depression; and (c) a multigenerational pedigree of manic symptoms, BD or depression.

2. Methods

2.1. Participants

One hundred and sixty-five children aged 8–11 participated in the Multi-Family Psychoeducational Psychotherapy (MF-PEP) study (Fristad et al., 2009), which assessed child diagnosis at baseline and 6-, 12- and 18-month follow-up visits. Twenty-seven children received a baseline diagnosis of BD-NOS and completed at least one follow-up assessment along with their parent or legal guardian. All children and parents gave written

assent/consent for data to be used for research purposes, and the study was approved by the local Institutional Review Board. Final diagnosis of the seven participants who did not complete all assessments was based on the last observation carried forward (LOCF; five children dropped out by 12 months, two converters and three nonconverters; two more children dropped out by 18 months, one converter and one nonconverter).

Children—Mean age was 9.7 years (SD=1.2 years); most were male ($n=21$, 77.7%) and White ($n=26$, 96.3%; $n=1$ African American, All had a co-morbid behavior disorder; 12 (44.4%) also had a co-morbid anxiety disorder.

Primary informants—Most were biological mothers ($n=23$, 85.2%); three were biological fathers (11.1%), one was a step-mother (3.7%).

Family members—Data were collected on 55 first-degree relatives (53 parents, two siblings) and 197 second-degree relatives (grandparents, aunts, and uncles).

Interviewers—Interviewers were post-doctoral study coordinators and graduate research associates in clinical psychology trained to reliability ($\kappa = 0.70$) prior to conducting independent interviews (Fristad et al., 2009).

2.2. Instruments

Three diagnostic assessment instruments were used, along with a detailed integrative diagnostic timeline of mood symptoms and episodes (Danner et al., 2009). Instruments administered to parents and children were: Children's Interview for Psychiatric Symptoms-Parent and Child Versions (P-ChIPS/ChIPS) (Weller et al., 1999; Weller et al., 1999), Young Mania Rating Scale (YMRS) (Young et al., 1978), and Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984). All three were utilized at baseline and 12 months; only mood rating scales were administered at 6 and 18 months. In addition, a detailed timeline of mood symptoms and episodes was created to more clearly capture the clinical presentation of each child. Standardized guidelines for gathering this information were used, including a template for recording specified information (Danner et al., 2009). Diagnoses were established via post-interview consensus diagnosis with two clinical child psychologists who independently reviewed comprehensive interview reports.

The Ohio State Adapted Family History-Research Diagnostic Criteria (FH-RDC) (Fristad, 1986) was used to collect baseline information concerning family history of 13 major psychiatric disorders in the probands' first- and second-degree adult (i.e., aged 18 or older) relatives. Data were recorded at symptom and diagnosis levels; those categorized with mania were included in the bipolar but not the depressive category. Adaptations from the original FH-RDC (Andreasen et al., 1977) were inclusion of eating disorder and anxiety disorder criteria. The FH-RDC has good to excellent reliability and validity for specific disorders, but lacks a high degree of sensitivity. It tends to underestimate psychopathology, particularly for mood disorders. Higher thresholds of diagnostic criteria improve its reliability. A genogram was constructed prior to assessing family history to establish the number of relatives on whom information was gathered.

2.3. Data analysis

Data were managed using SPSS version 19 statistical software (SPSS Inc., Chicago, IL). G*Power statistical software (Faul et al.) was used to calculate achieved power and determine the sample size needed for adequate power in future studies. All statistical tests were conducted at $\alpha=0.05$ individual level of significance.

Fisher's Exact test of independence, a non-parametric procedure designed for small sample sizes, was used to analyze the relationship between the two dichotomous, categorical variables in a 2×2 contingency table.

In addition, as measures of effect size, relative risk (RR) and odds ratios (OR) are reported. Because this research is considered exploratory, no adjustments were made for total number of analyses.

3. Results

3.1. Conversion rates from BD-NOS to BD-I or BD-II

Nine of 27 children (33%) converted from BD-NOS to BD-I ($n=8$) or BD-II ($n=1$) over 18 months. Five converted by 6 months, three more converted by 12 months, and one more converted by 18 months.

3.2. Family history rates

Table 1 summarizes descriptive statistics on first- and second-degree relatives and sample prevalence of BD and depression. No variable had distributions outside the acceptable range of skewness and kurtosis. The mean number of first-degree relatives was two (i.e., biological parents); only two participants had a sibling 18 years of age or older. The mean number of total relatives (first and second-degree) for a participant was 9.3 ($SD=3.5$, range=2–18). While this range was large, the distribution was normal and total number of relatives did not correlate with the outcome variable (i.e., diagnostic conversion) or any predictor variables.

Approximately 10% (24 of 252) of all first- and second-degree relatives had bipolar symptoms or diagnosis; approximately 31% (78 of 252) had depressive symptoms or diagnosis. Nearly half (48.1%) of the participants had one first-degree relative with BD symptoms or diagnosis; 40.7% had a relative with BD diagnosis, 7.4% had a relative with symptoms only. No participant had more than one first-degree relative with BD.

3.3. Family history as predictor of conversion

Table 2 summarizes analyses of family history variables as a risk factor for conversion. No results were statistically significant at the diagnosis or symptom level; however, it is important to bear in mind that power was quite low, ranging from 0.10 to 0.45, given the small sample size.

It is notable that six of 13 children (46.2%) who had a first-degree relative with bipolar symptoms converted, while only three of 14 (21.4%) children without this history converted ($OR=3.19$, $RR=2.19$). Similarly, six of 12 children (50%) with a loaded pedigree for depression diagnosis converted compared to three of 14 children (21.4%) without ($OR=3.67$, $RR=2.34$). Furthermore, six of 14 children (42.9%) with a multigenerational family history of depression diagnosis converted compared to three of 12 children (25%) without ($OR=2.25$, $RR=1.72$).

No participant had a loaded or multigenerational pedigree of bipolar symptoms or diagnosis; these hypotheses could not be tested. Post-hoc power analyses suggested sample sizes needed for adequate power ($\beta=0.80$) in future studies ranges is 70 (see Table 2).

4. Discussion

This study replicates previously reported rates of conversion from BD-NOS to BD-I or II among youth in the range of 29–38% (Birmaher et al., 2006; Birmaher et al., 2009) and further indicates both the instability of the BD-NOS diagnosis as well as its common

progression to a well-established bipolar diagnosis. Despite the absence of statistical significance, several trends emerged. Children in the current sample who had a first-degree relative with bipolar symptoms were more than twice as likely to convert to BD-I or II than those without one. Additionally, both a loaded pedigree and a multigenerational family history of depression diagnosis approximately doubled the likelihood of conversion.

Our finding that a strong family history of depression diagnoses predicted bipolar outcome echoes Gershon and colleagues (Gershon et al., 1982) finding that MDD diagnosis but not symptoms of depression predicted outcome. For BD, however, symptom-level analysis was more powerful than diagnosis-level analysis. Keeping in mind the probable under-diagnosis of BD in past generations, this is not surprising.

4.1. Limitations and future directions

This study's major limitation is the small sample size. Power to detect statistical significance was low; power analyses suggested a sample approximately 3–13 times larger would be appropriate.

Attrition further limited the number of participants for whom complete follow-up data were available. Lack of complete follow-up data resulted in a more conservative conversion estimate.

The lack of an established reliable and valid method of assessing family history of individuals under the age of 18 also meant most siblings were not included in family history analyses, thus limiting study sensitivity to the influence of mood disorders among first-degree relatives of child probands.

Future research on the familial relationship between BPSDs and other disorders (e.g., psychotic disorders, substance abuse, antisocial personality/conduct disorder, eating disorders, attention deficit hyperactivity disorder) is warranted. Most importantly, prospective longitudinal studies following children from their earliest phases of symptom presentation into adulthood will help elucidate what, if any, familial factors predict the emergence of BPSD across the lifespan.

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References

- American Psychiatric Association. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th ed.. American Psychiatric Association; Washington, DC: 2000. text revision
- Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry*. Oct.2006 63(10): 1139–1148. [PubMed: 17015816]
- Akiskal HS, Rosenthal RH, Rosenthal TL, Kashgarian M, Khani MK, Puzantian VR. Differentiation of primary affective illness from situational, symptomatic, and secondary depressions. *Archives of General Psychiatry*. 1979; 36(6):635–643. [PubMed: 444017]

- Akiskal H, Walker P, Puzantian V, King D, Rosenthal T, Dranon M. Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. *Journal of Affective Disorders*. 1983; 5(2):115–128. [PubMed: 6222091]
- Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria: reliability and validity. *Archives of General Psychiatry*. 1977; 34:1229–1235. [PubMed: 911222]
- Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry*. 2006; 63(2):175–183. [PubMed: 16461861]
- Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *American Journal of Psychiatry*. 2009; 166(7):795–804. [PubMed: 19448190]
- Bader C, Dunner D. Bipolar disorder not otherwise specified in relation to the bipolar spectrum. *Bipolar Disorders*. 2007; 9:860–867. [PubMed: 18076535]
- Danner S, Fristad MA, Arnold LE, Youngstrom EA, Birmaher B, Horwitz SM, et al. Early-onset bipolar spectrum disorders: diagnostic issues. *Clinical Child and Family Psychology Review*. 2009; 12(3):271–293. [PubMed: 19466543]
- Fristad MA, Verducci JS, Walters K, Young ME. Impact of multifamily psychoeducational psychotherapy in treating children aged 8–12 years with mood disorders. *Archives of General Psychiatry*. 2009; 66(9):1013–1021. [PubMed: 19736358]
- Fristad, M. The Ohio State Adaptation of the Family History—Research Diagnostic Criteria. The Ohio State University; 1986. Unpublished Document
- Faul F, Erdfelder E, Lang A-G, Buchner AG. Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavioral Research Methods*. 2007; 39:175–191.
- Gershon E, Baron M, Leckman JF. Genetic models of the transmission of affective disorders. *Journal of Psychiatric Research*. 1975; 12(4):301–317.
- Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Archives of General Psychiatry*. 1982; 39(10):1157–1167. [PubMed: 7125846]
- Hodgins S, Faucher B, Zarac A, Ellenbogen M. Children of parents with bipolar disorder: a population at high risk for major affective disorders. *Child and Adolescent Psychiatric Clinics of North America*. 2002; 11(3):533–554. [PubMed: 12222082]
- Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disorders*. 2000; 2:281–293. [PubMed: 11249806]
- Poznanski EO, Grossman J, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the children's depression rating scale. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1984; 23(2):191–197.
- Rudolph, K.; Hammen, C.; Daley, S. Mood disorders.. In: Wolfe, DA.; Mash, EJ., editors. *Behavioral and Emotional Disorders in Adolescents: Nature, Assessment, and Treatment*. Guilford Publications; New York, NY: 2006. p. 300-342.
- Todd RD, Neuman R, Geller B, Fox LW, Hickok J. Genetic studies of affective disorders: should we be starting with childhood onset probands? *Journal of the American Academy of Child and Adolescent Psychiatry*. 1993; 32(6):1164–1171. [PubMed: 8282660]
- Weller, EB.; Weller, RA.; Rooney, MT.; Fristad, MA. Children's Interview for Psychiatric Syndromes-Parent Version (P-ChIPS). American Psychiatric Press; Washington, DC: 1999.
- Weller, EB.; Weller, RA.; Fristad, MA.; Rooney, MT. Children's Interview for Psychiatric Syndromes (ChIPS). American Psychiatric Press; Washington, DC: 1999.
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*. 1978; 133:429–435. [PubMed: 728692]

Table 1

Number of relatives and prevalence of mood disorder among relatives inquired about in the Ohio State University Adapted Family History Research Diagnostic Criteria interview.

	<i>n</i>	Mean	SD	Range	Min	Max
Total number of relatives assessed	252	9.33	3.50	16	2	18
Number of first-degree relatives	55	2.04	0.34	2	1	3
Mothers	27	1.00	0	0	1	1
Fathers	26	0.96	0.19	1	0	1
Siblings	2	0.07	0.27	1	0	1
Offspring	0	0.00	0	0	0	0
Number of second-degree relatives	197	7.30	3.45	16	0	16
Maternal grandparents	50	1.85	0.53	2	0	2
Maternal aunts and uncles	50	1.85	1.90	7	0	7
Paternal grandparents	50	1.85	0.53	2	0	2
Paternal aunts and uncles	47	1.74	1.77	8	0	8
BD Sx or Dx	24	0.92	0.80	3	0	3
First-degree relatives	13	0.48	0.51	1	0	1
Second-degree relatives	11	0.42	0.50	1	0	1
BD Dx	16	0.62	0.64	2	0	2
First-degree relatives	11	0.41	0.50	1	0	1
Second-degree relatives	5	0.19	0.40	1	0	1
Depression Sx or Dx	78	2.89	1.63	7	0	7
First-degree relatives	30	1.11	0.51	2	0	2
Second-degree relatives	48	1.85	1.43	5	0	5
Depression Dx	64	2.37	1.64	6	0	6
First-degree relatives	26	0.96	0.52	2	0	2
Second-degree relatives	38	1.46	1.39	5	0	5
Proportion of relatives affected						
BD Sx or Dx	–	10%	0.09	0.33	0	0.33
BD Dx	–	6%	0.07	0.25	0	0.25
Depression Sx or Dx	–	33%	0.19	0.75	0	0.75
Depression Dx	–	27%	0.18	0.75	0	0.75

Table 2

Family history variables as a risk factor for predicting conversion from BD-NOS to BD-I or BD-II in children ($N=27$).

	Fisher's exact	p-value	1-tailed/2-tailed	OR(CI)	RR	Power	N needed for power of .80
1 First-degree relative							
BD Dx or Sx		0.17/0.24		3.14 (0.59–16.85)	2.19	0.39	92
BD Dx only		0.55/1.00		1.26 (0.25–6.36)	1.16	0.11	2473
Loaded							
Depression Dx or Sx		0.40/0.68		1.78 (0.33–9.55)	1.47	0.18	355
Depression Dx only		0.13/0.22		3.67 (0.66–20.19)	2.34	0.45	70
Multigenerational							
Depression Dx or Sx		0.64/1.00		1.09 (0.20–6.01)	1.06	0.10	15,456
Depression Dx only		0.30/0.43		2.25 (0.42–12.09)	1.72	0.25	177

BD=bipolar disorder; OR=odds ratio; RR=relative risk; Dx=diagnosis; Sx=symptoms.