Reference Materials on Thermoregulatory Sleep Dysregulation Disorder (TSDD) also known as "FOH"

This packet is a companion to CMHRC's materials outlining the diagnosis of Thermoregulatory Sleep Dysregulation Disorder (TSDD), which is also commonly referred to as "FOH".

The research papers that follow have all been cited in CMHRC's review of current literature on bipolar disorder and TSDD/FOH. Each paper can be found online and accessed for free by the general public. The copyrights belong wholly to the authors and the publications in which they were originally published. CMHRC makes no claim of ownership or authorship.

CMHRC does not charge any fee for access to these research papers. They are collected here only as a convenience as they are all cited in our summary packet on the TSDD/FOH diagnosis.

Free access to these papers can also be found through the National Library of Medicine website, PubMed (which is made available through National Institutes of Health), Hapres academic publishing, and/or other publicly accessible websites.

CMHRC's Role

Children's Mental Health Resource Center is a nonprofit organization that provides guidance and resources for early identification and management of mood disorders, bipolar disorder, and the newly identified phenotype of bipolar dubbed "FOH".

Early intervention is the best tool for the long term successful treatment of mental illness. CMHRC believes that through early, accurate diagnosis and the implementation of effective treatment plans based on reputable research, children with these disorders have the best chance of achieving long term stability.

Through education, outreach, advocacy, and support programs CMHRC works directly with families whose children and adolescents live with mood disorders, bipolar disorder, and "FOH".

Through these same programs and services, CMHRC provides resources and support to the physical and mental healthcare providers who work with families in their professional practice.

CMHRC does not provide treatment, but works to:

- Raise awareness among families and professionals of mood disorders, bipolar disorder, and "FOH" in children, teens, and young adults;
- Raise awareness among professionals on how to identify and treat these disorders;
- Increase access to accurate diagnosis and effective treatment;
- Provide support to families living with mood disorders, bipolar disorder, and "FOH",
- Provide support to professionals who treat mood disorders, bipolar disorder, and "FOH".

CHILDREN'S MENTAL HEALTH RESOURCE CENTER

Contents

Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study

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abstract

BACKGROUND: Lithium is a benchmark treatment for bipolar disorder in adults. Definitive studies of lithium in pediatric bipolar I disorder (BP-I) are lacking.

METHODS: This multicenter, randomized, double-blind, placebo-controlled study of pediatric participants (ages 7–17 years) with BP-I/manic or mixed episodes compared lithium (n = 53) versus placebo (n = 28) for up to 8 weeks. The a priori primary efficacy measure was change from baseline to the end of study (week 8/ET) in the Young Mania Rating Scale (YMRS) score, based on last-observation-carried-forward analysis.

RESULTS: The change in YMRS score was significantly larger in lithium-treated participants (5.51 [95% confidence interval: 0.51 to 10.50]) after adjustment for baseline YMRS score, age group, weight group, gender, and study site (P = .03). Overall Clinical Global Impression–Improvement scores favored lithium (n = 25; 47% very much/much improved) compared with placebo (n = 6; 21% very much/much improved) at week 8/ET (P = .03). A statistically significant increase in thyrotropin concentration was seen with lithium (3.0 $\pm$ 3.1 mIU/L) compared with placebo (–0.1 $\pm$ 0.9 mIU/L; $P < .001$). There was no statistically significant between-group difference with respect to weight gain.

CONCLUSIONS: Lithium was superior to placebo in reducing manic symptoms in pediatric patients treated for BP-I in this clinical trial. Lithium was generally well tolerated in this patient population and was not associated with weight gain, distinguishing it from other agents commonly used to treat youth with bipolar disorder.

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Dr Findling was responsible for study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtaining funding; administrative, technical, and/or material support; and study supervision. Dr Findling had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Dr Robb was responsible for study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtaining funding; administrative, technical, and/or material support; and study supervision. Dr McNamara was responsible for acquisition of data and administrative, technical, and/or material support.

WHAT'S KNOWN ON THIS SUBJECT: Strictly-defined pediatric bipolar I disorder (BP-I) is a serious condition. Although lithium is a benchmark treatment and has shown effectiveness in adults for decades, no definitive efficacy or long-term safety studies had been performed in pediatric patients with BP-I.

WHAT THIS STUDY ADDS: This study provides evidence to support the efficacy of lithium in the acute treatment of youths with BP-I who are currently in a manic or mixed state. Lithium had an adverse effect profile that was acceptable for most patients.

Bipolar I disorder (BP-I) is a highly impairing mood disorder that often has its onset before adulthood.[1] It is a psychiatric condition that occurs in pediatric patients worldwide.[2] This chronic disorder is characterized by periods of spontaneous, abnormally elevated mood and abnormally irritable mood.[3] BP-I is associated with substantial disability,[4] suicide attempts,[5,6] reduced quality of life, and significant functional impairment.[7–9]

Lithium has long been a benchmark treatment of adults with BP-I.[10–14] Despite lithium's use for BP-I in adults, definitive placebo-controlled, methodologically stringent studies of efficacy have not been available for children.[15]

The Best Pharmaceuticals for Children Act was signed into law in 2002 and re-authorized in 2007 under the Food and Drug Administration Amendments Act and in 2012 under the Food and Drug Administration Safety and Innovation Act.[16] The law incorporates as its key legislative goals: (1) prioritizing the study of off-patent drugs used in children; and (2) sponsoring clinical trials when a pharmaceutical company declines to perform them. In 2005, a written request from the US Food and Drug Administration was sent to the National Institutes of Health, who, in turn, developed a contract with a consortium of experts in the field of child and adolescent psychiatry to conduct a rigorous and comprehensive set of clinical studies of lithium in children with BP-I. Hence, the Collaborative Lithium Trials were conducted.

One of the foremost purposes of the Collaborative Lithium Trials was to examine the acute efficacy and long-term safety of lithium in participants aged 7 to 17 years with BP-I. After establishing the pharmacokinetics, the empirically determined dosing strategy, and tolerability through an initial set of studies,[17,18] the first randomized, double-blind, placebo-controlled lithium acute efficacy trial was conducted in a different patient sample. The present article describes the key findings of that trial and the impact the results may have on pediatric mental health.

METHODS

We conducted a multicenter, randomized, placebo-controlled outpatient trial to examine lithium in the acute treatment of pediatric patients with BP-I. Details of the study design and methods are presented elsewhere[19] and are briefly summarized here. Outpatient participants were enrolled at 1 of 10 academic medical centers in the United States that are experienced in pediatric psychiatric care. The study duration for each participant in this efficacy clinical trial was up to 8 weeks, with visits completed at weeks 1, 2, 3, 4, 6, and 8 and telephone assessments at day 3 of week 1, week 5, and week 7. The first participant was enrolled on June 2, 2010, and date of study completion for the last participant was February 7, 2013.

Study Participants

Children aged 7 to 17 years meeting unmodified *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for BP-I currently in a manic or mixed episode, scoring ≥20 on the Young Mania Rating Scale (YMRS),[20] having a negative drug screen at baseline and remaining drug-free through the study period, and willing and clinically able to undergo a washout period for all psychotropic medications were eligible. Children were ineligible if they: were clinically stable on a medication regimen for BP-I; diagnosed with schizophrenia or schizoaffective disorder, a pervasive developmental disorder, anorexia nervosa, bulimia nervosa, obsessive-compulsive disorder, substance dependence, symptoms of mania that were attributable to a general medical condition or secondary to use of medications or general medical condition including neurologic disease, diabetes mellitus, thyroid dysfunction, or renal dysfunction that might be adversely affected by lithium; had clinically significant abnormal laboratory assessments that could influence the efficacy or safety of lithium or would complicate interpretation of study results; had evidence of serious homicidal/suicidal ideation or active hallucinations and delusions such that in the treating physician's opinion it would not be appropriately safe for the subject to participate in this study; or had concomitant prescription of over-the-counter medication or nutritional supplements that would interact with lithium or affect the participant's physical or mental status.

Initially, the prescription of concomitant psychostimulants was precluded. However, starting in June 2011, to enhance recruitment and retention, participants with comorbid attention-deficit/hyperactivity disorder were able to receive psychostimulants after 4 weeks of double-blind therapy at the treating physician's discretion. Melatonin (up to 3 mg) at bedtime was permitted to treat insomnia.

Institutional Review Board Review and Informed Consent

Local institutional review board approval of the protocol, informed consent, advertising, and all amendments were obtained at each of the 10 study sites before implementation. Before the initiation of any study-related procedures, the informed consent statement was signed by the participant's parent or legal guardian and by the person who was authorized to administer the informed consent. Children who could read and understand the assent form were asked to give written assent.

Diagnostic Procedures

Eligible participants underwent a psychiatric interview with a board-certified or board-eligible child and adolescent psychiatrist. This interview was followed by an assessment with an interviewer/rater trained on study-specific procedures using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)[21] to confirm the clinician's diagnosis.

Initial training presentations were provided for the K-SADS-PL, the YMRS, the Children's Depression Rating Scale–Revised (CDRS-R),[22,23] and the Columbia Suicide Severity Rating Scale[24] for raters across all 10 sites. Raters were considered trained if they scored within 20% of the gold standard score for the YMRS and CDRS-R videos (established by the lead clinical site Principal Investigator) in addition to completing a written examination regarding administration of the K-SADS-PL. Inter-rater reliability was completed on the CDRS-R and the YMRS every 6 months to ensure consistency between raters at all sites.

Randomization, Masking, and Drug Administration

Participants were enrolled into the study and were randomized to receive lithium or matching placebo in a 2 (lithium):1 (placebo) allocation ratio. Stratification factors included study site, age at randomization (7–11 years and 12–17 years), and gender (male and female). The randomization list was created by an unblinded BPCA data coordinating center (DCC) statistician. Unblinded site staff members were provided randomization assignments via an electronic data capture system.

The dosing of lithium used in the present study was based on previous research conducted by this investigative group.[17,18] The starting dose of lithium (supplied as 300-mg, regular-release capsules) was either 600 or 900 mg/d. Participants weighing <30 kg started with 600 mg/d; all other participants began lithium therapy with 900 mg/d. Dose increases of 300 mg/d could occur at study visits and via telephone call during the middle of the first week of randomized treatment unless the participant had the following: had met dosing response criteria (defined as a Clinical Global Impression–Improvement scale [CGI-I][25] score ≤ 2 and a 50% decrease in the YMRS score from baseline assessment); experienced ≥ 1 adverse effect that significantly affected functioning that was at least of moderate severity; had a serum lithium level >1.4 mEq/L; or if the dose exceeded 40 mg/kg/d (with the exception of participants weighing <23 kg, who could receive up to 900 mg/d). Participants randomized to receive placebo were preassigned to a maximum dose at randomization to maintain the integrity of the blind. Adherence to study medication was monitored by using a dosing diary and pill counts.

Study Assessments

The a priori primary outcome measure was the change from baseline to the end of study (week 8/early termination [ET]) on the YMRS score, based on last-observation-carried-forward (LOCF) values. Beginning at baseline, psychometric assessments performed at study visits included the YMRS, the CDRS-R, and the Clinical Global Impression–Severity scale (CGI-S).[24] Starting at week 1, the CGI-I was obtained at study visits. The Columbia Suicide Severity Rating Scale was completed at each study visit to assess for suicidal behavior and ideation by a trained rater. Baseline scores were compared with subsequent scores during the 8-week trial. Treatment safety at each visit was evaluated based on the incidence of adverse events (AEs), treatment-emergent AEs, serious AEs, treatment-emergent AEs leading to study drug discontinuation, clinically significant laboratory findings, vital signs, electrocardiogram investigations, physical examination abnormalities, and trough lithium serum levels. Lithium levels were obtained at all study visits.

AE Monitoring

Participants were monitored for the presence of treatment-emergent AEs by open-ended inquiry and use of the Side Effects Form for Children and Adolescents,[26] the Neurological Examination for Lithium,[18] and the Neurological Rating Scale[27] at each study visit. A 13-item expanded version of the Neurological Rating Scale was used to assess for potential additional extrapyramidal adverse effects. These additional items include: (1) cogwheeling; (2) acute dystonic reaction; and (3) subjective sense of stiffness.

Items from the Side Effects Form for Children and Adolescents, the Neurological Examination for Lithium, the Neurological Rating Scale, or open-ended inquiry that were reported as being present since the last visit were documented at each study visit. The study physician who conducted the visit determined whether the effects that were reported constituted an AE and whether the AE was related to study medication.

The intensity or severity of AEs was graded as follows: mild (awareness of sign or symptom but easily tolerated; not expected to have a clinically significant effect on the participant's overall health and well-being; not likely to require medical attention); moderate (discomfort enough to cause interference with usual activity or affects clinical status; may require medical intervention); or severe (incapacitating or significantly affecting clinical status; likely

requires medical intervention and/or close follow-up).

Statistical Analyses and Sample Size Determinations

Sample size determination was based on interim conditional power analyses. These analyses suggested that with a total sample size of 100, there would be 94% power to detect a statistically significant difference in the mean change from baseline to week 8/ET in YMRS scores in the 2 treatment arms, based on LOCF values.

Efficacy variables that were based on assessment instruments administered over the course of weekly assessments in the study, including the YMRS, the CDRS-R, and the Children's Global Assessment Scale (CGAS),[28] were analyzed primarily on the basis of mean change from baseline to end-of-study scores according to LOCF methods. These changes were assessed by using an analysis of covariance model, with change from baseline score as the dependent variable, baseline score as a covariate, and age stratum, gender, weight (<30 kg and ≥30 kg), study site (pooled), and treatment group as factors.

The CGI-S and CGI-I (overall illness scores) are measured on a Likert scale and were analyzed by using a logistic regression model. A reduction of at least 2 points from baseline to week 8/ET on the CGI-S was considered an improvement for this measure. A score of 1 or 2 on the CGI-I measured at week 8/ET was classified as an improvement on this scale. Independent factors in the logistic regression model were age stratum, gender, weight (<30 kg or ≥30 kg), and treatment group.

The categorical end points of response and remission were compared according to treatment group. Response was defined as a reduction in baseline YMRS score ≥50% and a CGI-I score of 1 or 2. Remission was defined as a YMRS score ≤12 and a CGI-S score ≤2. Cochran-Mantel-Haenszel tests were performed to determine if there was a significant difference in proportions between the treatment groups for each of these end points.

All analyses were conducted by using SAS version 9.2 or higher (SAS Institute, Inc, Cary, NC).

RESULTS

Study Participants and Characteristics

A total of 153 participants were screened for possible inclusion into this clinical trial. Of these 153, 81 (53%) were randomized to receive lithium (n = 53) or placebo (n = 28) based on a 2:1 allocation ratio. Fig 1 summarizes participants screened and enrolled into the study. Enrollment across the sites ranged from 1 patient to 24 patients randomized to study.

Table 1 displays the baseline characteristics of the participants. There were no statistically significant differences between the lithium and placebo groups regarding the baseline variables of age group, gender, race, and ethnicity. Furthermore, there were no statistically significant

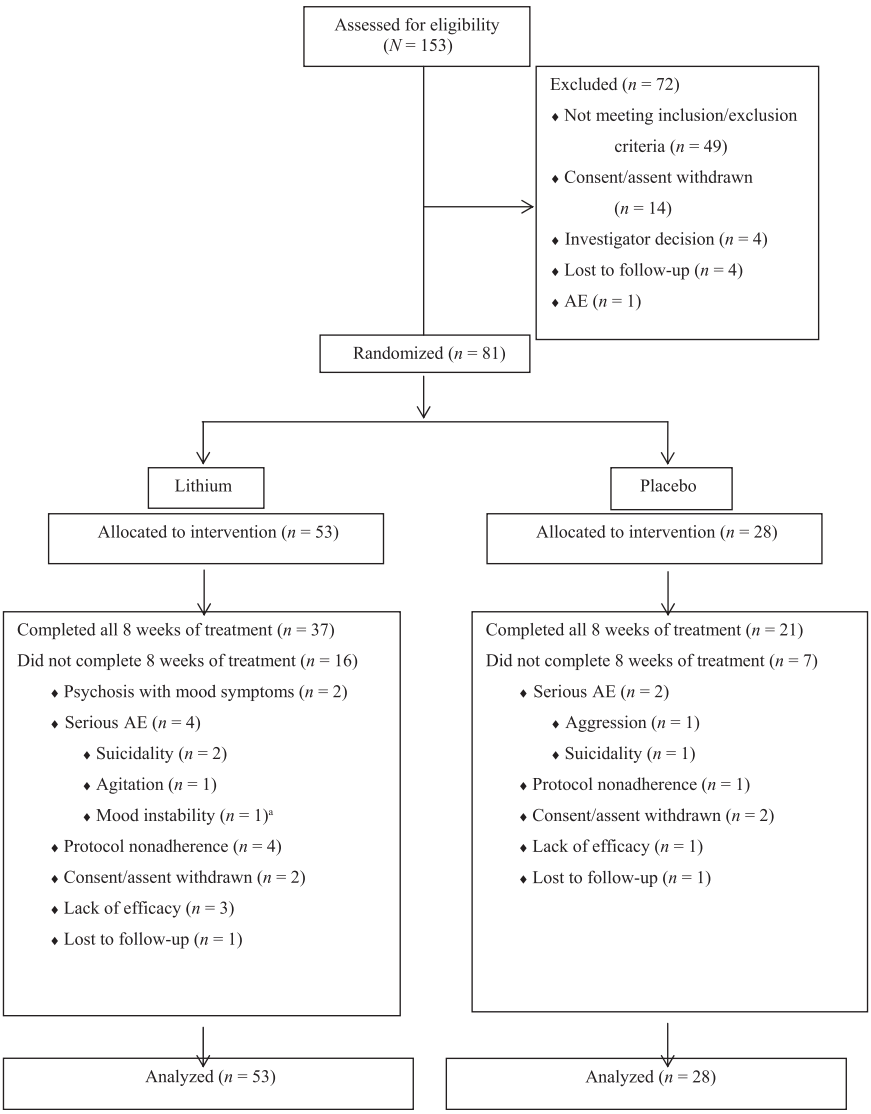

FIGURE 1
Participant flow. [a]Participant also experienced previous serious AE of aggression.

TABLE 1 Baseline Demographic Characteristics, Symptoms, and Comorbid Diagnoses

Characteristic	7–11 Years of Age		12–17 Years of Age		Total	
	Lithium (n = 32)	Placebo (n = 17)	Lithium (n = 21)	Placebo (n = 11)	Lithium (n = 53)	Placebo (n = 28)
Age at baseline, y						
Mean ± SD	9.5 ± 1.6	9.1 ± 1.3	14.6 ± 1.5	14.5 ± 1.6	11.5 ± 2.9	11.2 ± 3.0
Median (Min–Max)	9.8 (7.3–11.9)	9.0 (7.0–11.6)	14.1 (12.3–17.3)	14.3 (12.5–16.7)	11.3 (7.3–17.3)	10.6 (7.0–16.7)
Gender, n (%)						
Male	14 (43.8)	10 (58.8)	8 (38.1)	5 (45.5)	22 (41.5)	15 (53.6)
Female	18 (56.3)	7 (41.2)	13 (61.9)	6 (54.5)	31 (58.5)	13 (46.4)
Ethnicity, n (%)						
Hispanic or Latino	6 (18.8)	1 (5.9)	3 (14.3)	2 (18.2)	9 (17.0)	3 (10.7)
Not Hispanic or Latino	26 (81.3)	16 (94.1)	17 (81.0)	8 (72.7)	43 (81.1)	24 (85.7)
Not reported	0	0	1 (4.8)	1 (9.1)	1 (1.9)	1 (3.6)
Race, n (%)						
White	18 (56.3)	10 (58.8)	12 (57.1)	4 (36.4)	30 (56.6)	14 (50.0)
African American	10 (31.3)	6 (35.3)	5 (23.8)	5 (45.5)	15 (28.3)	11 (39.3)
Asian	0	0	2 (9.5%)	0	2 (3.8)	0
>1 race	3 (9.4)	1 (5.9)	1 (4.8)	1 (9.1)	4 (7.5)	2 (7.1)
Not reported	1 (3.1)	0	1 (4.8)	1 (9.1)	2 (3.8)	1 (3.6)
Most recent episode, n (%)						
Manic	15 (46.9)	10 (58.8)	8 (38.1)	8 (72.7)	23 (43.4)	18 (64.3)
Mixed	17 (53.1)	7 (41.2)	13 (61.9)	3 (27.3)	30 (56.6)	10 (35.7)
YMRS total score						
Mean ± SD	28.9 ± 4.6	31.4 ± 6.3	30.5 ± 6.9	27.9 ± 4.9	29.5 ± 5.6	30.0 ± 6.0
CDRS-R total score						
Mean ± SD	34.2 ± 8.8	40.5 ± 11.3	38.2 ± 11.7	34.6 ± 7.3	35.8 ± 10.1	38.2 ± 10.2
CGI-S score (overall illness), n (%)						
4, moderately ill	17 (53.1)	4 (23.5)	10 (47.6)	8 (72.7)	27 (50.9)	12 (42.9)
5, markedly ill	13 (40.6)	12 (70.6)	9 (42.9)	3 (27.3)	22 (41.5)	15 (53.6)
6, severely ill	2 (6.3)	1 (5.9)	2 (9.5)	0	4 (7.5)	1 (3.6)
CGAS score						
Mean ± SD	51.2 ± 6.2	50.4 ± 7.2	47.7 ± 6.9	49.6 ± 4.3	49.8 ± 6.7	50.1 ± 6.1
Columbia Suicide Severity Rating Scale–Lifetime Ratings, n (%)						
Suicidal ideation						
Thoughts of their death	16 (50.0)	8 (47.1)	12 (57.1)	6 (54.6)	28 (52.8)	14 (50.0)
Nonspecific suicidal thoughts	4 (12.5)	3 (17.7)	6 (28.6)	1 (9.1)	10 (18.9)	4 (14.3)
Active thoughts of methods but no clear plan	1 (3.1)	1 (5.9)	2 (9.5)	0	3 (5.7)	1 (3.6)
Active ideation with plan	1 (3.1)	3 (17.7)	3 (14.3)	2 (18.2)	4 (7.6)	5 (17.9)
History of suicide attempts	0	1 (5.9)	1 (4.8)	1 (9.1)	1 (1.9)	2 (7.1)
History of interrupted attempts	0	1 (5.9)	2 (9.5)	0	2 (3.8)	1 (3.6)
History of aborted attempts	0	1 (5.9)	0	0	0	1 (3.6)
Comorbid diagnoses, n (%)						
ADHD	22 (68.8)	11 (64.7)	12 (57.1)	7 (63.6)	34 (64.2)	18 (64.3)
Disruptive behavior	7 (21.9)	3 (17.7)	4 (19.1)	3 (27.3)	11 (20.8)	6 (21.4)
Enuresis	1 (3.1)	2 (11.8)	0	0	1 (1.9)	2 (7.1)
Anxiety disorder	8 (25.0)	5 (29.4)	6 (28.6)	0	14 (26.4)	5 (17.9)
Other[a]	0	2 (11.8)	1 (4.8)	0	1 (1.9)	2 (7.1)

ADHD, attention-deficit/hyperactivity disorder; Min–Max, minimum–maximum.

[a] Other includes 1 each of marijuana abuse, motor tic disorder, and trichotillomania.

differences between treatment groups at baseline with regard to the most recent episode (manic or mixed) and YMRS, CDRS-R, CGAS, or CGI-S overall illness scores.

There was no statistically significant difference between the treatment groups with respect to length of study participation. The mean ± SD length of study participation for lithium-treated participants and placebo participants was 47.5 ± 16.6 days and 48.6 ± 15.3 days, respectively. The mean lithium serum level at study's end was 0.98 ± 0.47 mEq/L.

Details regarding end-of-study lithium dosing are summarized in Table 2.The mean daily dose for participants aged 7 to 11 years (n = 49) was 1292 ± 420 mg and 1716 ± 606 mg for participants aged 12 to 17 years (n = 32). With regard to weight, the mean daily dose was 956 ± 225 mg for participants weighing <30 kg (n = 16) and 1583 ± 524 mg for participants weighing ≥30 kg (n = 65).

The overall mean adherence rate for medication dosing was 91.9 ± 11.8%. The adherence rates for the lithium and placebo groups were

TABLE 2 Dosing and Weight at Last Study Visit According to Randomized Study Group

Variable	Lithium (n = 53)	Placebo (n = 28)	Total (N = 81)
Dose, mg/d			
Mean ± SD	1483 ± 584	1414 ± 454	1459 ± 540
Median (Min–Max)	1500 (300–3600)	1350 (600–2700)	1500 (300–3600)
Dose, mg/kg/d			
Mean ± SD	30.5 ± 8.7	29.2 ± 10.1	30.0 ± 9.2
Median (Min–Max)	30.0 (5.9–50.0)	27.6 (10.0– 47.1)	29.0 (5.9–50.0)
Weight, kg			
Mean ± SD	51.8 ± 22.5	52.7 ± 19.8	52.1 ± 21.5
Median (Min–Max)	47.2 (19.5–115.7)	50.5 (25.8–105.7)	47.8 (19.5–115.7)

End dose is the last nonzero dose reported. Min–Max, minimum–maximum.

92.0 ± 11.8% and 91.6 ± 12.1%, respectively.

Mania Response

The mean YMRS LOCF score at week 8 for lithium was 17.8 ± 11.0, and for placebo it was 22.3 ± 9.7. The mean change from baseline to week 8 LOCF is illustrated in Figure 3. The change in YMRS score at week 8 (ie, the primary efficacy measure) was significant in favor of lithium (P = .03). After adjusting for baseline YMRS score, age group, weight group, gender, and study site, the treatment effect size was 5.51 (95% confidence interval: 0.51 to 10.50).

The adjusted standardized effect size (Cohen's d) and corresponding 95% confidence interval, adjusting for baseline factors in the primary efficacy analysis, was 0.53 (0.06 to 0.99).[29] The unadjusted standardized effect size was 0.37 (–0.10 to 0.83).

Secondary Measures

For the CDRS-R, the mean decrease in scores (reflecting reduced depressive symptoms) was 5.5 ± 12.2 on lithium and 6.8 ± 8.5 on placebo (P = .49). CGAS scores increased (indicative of improved global functioning) for patients receiving lithium (9.5 ± 13.8) and for those receiving placebo (8.5 ± 12.1) (P = .63). Scores in 22 (42%) of the lithium group participants decreased at least 2 points (from baseline to week 8/ET) on the CGI-S for overall illness severity, whereas 6 (21%) participants receiving placebo decreased by at least 2 points. There was no statistically significant between-group difference (P = .11). However, overall CGI-I scores favored lithium (n = 25; 47% very much/much improved) compared with placebo (n = 6; 21% very much/much improved) at week 8/ET (P = .03).

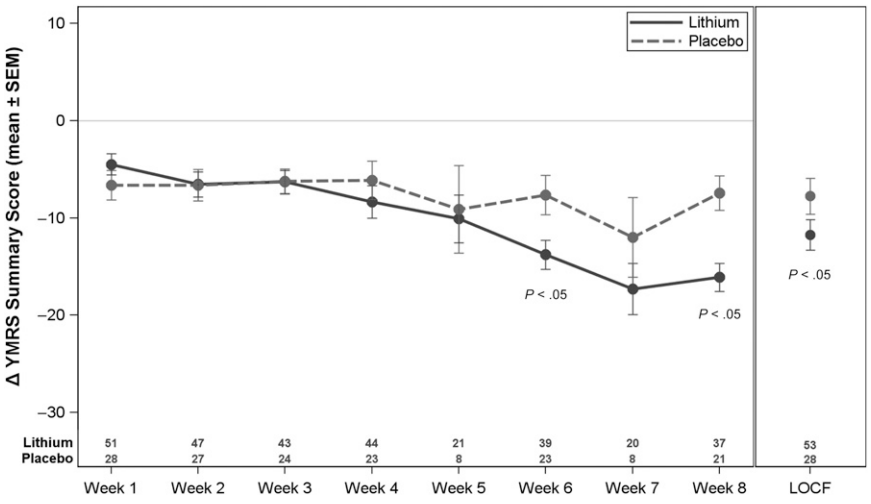

FIGURE 2
Change in YMRS summary score according to visit in the intention-to-treat population. Baseline was defined as the first visit of the efficacy phase. Visits at weeks 5 and 7 were changed from clinic-based visits to telephone calls with a protocol amendment on July 15, 2011 (with no YMRS data collected).

Response and Remission

The number of participants meeting a priori response criteria (reduction in baseline YMRS score ≥50% and CGI-I score of 1 or 2) was 17 (32%) for lithium and 6 (21%) for placebo. The number of participants meeting criteria for remission (YMRS score ≤12 and CGI-S score ≤2) at the end of study was 14 (26%) for lithium and 4 (14%) for placebo. There was no statistically significant difference between treatment groups for either response or remission.

Adverse Events

No participants discontinued the study due to lack of tolerability. The mean number of AEs per participant was 6.4 (7.7 in the lithium group and 4.0 in the placebo group).

Seven AEs met the definition of a serious AE. These 7 events occurred among 6 participants (5 events in 4 lithium participants and 2 events in 2 placebo participants). None of the serious AEs were believed to be related to study medication.

Two lithium-treated participants discontinued the study due to persistent psychosis. Two lithium participants and 1 placebo participant discontinued because of suicidality; all 3 of these discontinuations were considered unrelated to the study medication. Three additional AEs led to study discontinuation: 1 lithium participant with agitation, 1 lithium participant with mood instability, and 1 placebo participant with aggressive behavior. All of these discontinuations were unrelated to study medication. Table 3 lists those AEs occurring at a rate of ≥5% and twice as frequently on lithium as placebo. Most AEs were mild to moderate in severity.

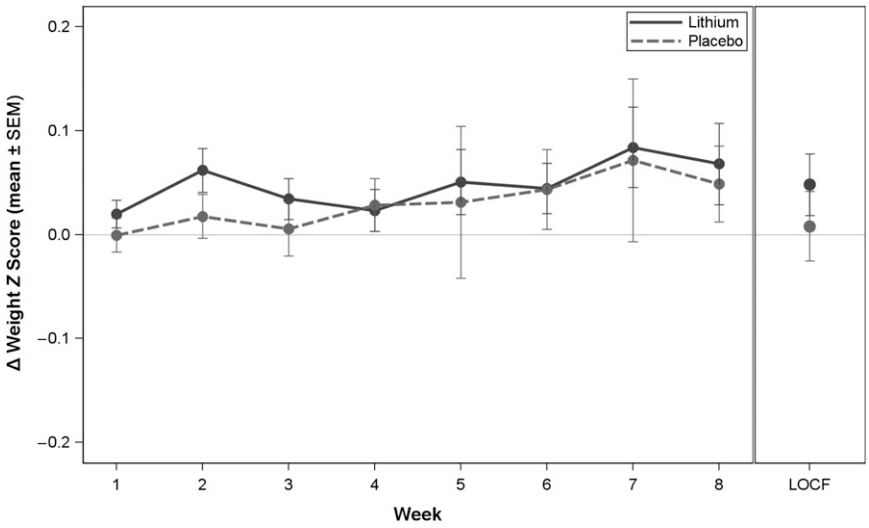

FIGURE 3
Change in weight *z* score during the efficacy phase. Change score is the week value minus the baseline value; baseline is defined as the first visit of the efficacy phase.

The most common AEs with lithium were vomiting (n = 24 [45%]), nausea (n = 23 [43%]), and headache (n = 19 [36%]). With placebo, headache (n = 9 [32%]), upper abdominal pain (n = 9 [32%]), and nausea and increased appetite (both at n = 5 [18%]) were most common. Fourteen of the 24 lithium-treated participants who experienced vomiting had their first episode during week 1. The dose was reduced in 12 of the 24 participants after a vomiting episode. The mean ± SD length of time from onset of vomiting to resolution (or end of phase) for lithium-treated participants was 7.3 ± 11.4 days; the mean length of time for resolution of nausea was 14.7 ± 17.3 days.

A weight gain of 0.9 ± 1.6 kg was reported in the lithium-treated participants and a weight gain of 1.2 ± 1.7 kg was observed in participants receiving placebo (Figure 3). There was no statistically significant between-group difference with respect to weight gain. A statistically significant increase in thyrotropin concentration of 3.0 ± 3.1 mIU/L was observed in those participants who received lithium, compared with −0.1 ± 0.9 mIU/L in participants receiving placebo ($P < .001$).

No participants discontinued treatment as a result of any clinically significant findings related to vital signs, physical examination, or electrocardiography.

DISCUSSION

The present study comprises the largest prospective, randomized, double-blind, placebo-controlled study to-date of lithium in youth aged 7 to 17 years with BP-I mixed or

TABLE 3 AEs Seen at a Rate of ≥5% ($n \geq 5$) in the Total Population and Twice as Frequently With Lithium as Placebo According to Age Strata and Treatment Group

System Organ Class/Preferred Term	7–11 Years of Age		12–17 Years of Age		Total	
	Lithium (n = 32)	Placebo (n = 17)	Lithium (n = 21)	Placebo (n = 11)	Lithium (n = 53)	Placebo (n = 28)
Eye disorders						
Blurred vision	4 (12.5%)	0	1 (4.8%)	0	5 (9.4%)	0
Gastrointestinal disorders						
Abdominal pain	4 (12.5%)	0	2 (9.5%)	1 (9.1%)	6 (11.3%)	1 (3.6%)
Diarrhea	10 (31.3%)	3 (17.6%)	5 (23.8%)	1 (9.1%)	15 (28.3%)	4 (14.3%)
Nausea	12 (37.5%)	3 (17.6%)	11 (52.4%)	2 (18.2%)	23 (43.4%)	5 (17.9%)
Vomiting	15 (46.9%)	3 (17.6%)	9 (42.9%)	0	24 (45.3%)	3 (10.7%)
General disorders and administration site conditions						
Fatigue	0	0	5 (23.8%)	1 (9.1%)	5 (9.4%)	1 (3.6%)
Thirst	12 (37.5%)	0	3 (14.3%)	3 (27.3%)	15 (28.3%)	3 (10.7%)
Laboratory tests						
Blood thyroid-stimulating hormone increased	4 (12.5%)	0	5 (23.8%)	0	9 (17.0%)	0
Metabolism and nutrition disorders						
Decreased appetite	5 (15.6%)	1 (5.9%)	0	0	5 (9.4%)	1 (3.6%)
Nervous system disorders						
Dizziness	7 (21.9%)	0	5 (23.8%)	2 (18.2%)	12 (22.6%)	2 (7.1%)
Sedation	6 (18.8%)	0	0	0	6 (11.3%)	0
Tremor	9 (28.1%)	2 (11.8%)	8 (38.1%)	0	17 (32.1%)	2 (7.1%)
Renal and urinary disorders						
Pollakiuria (abnormally frequent urination)	10 (31.3%)	0	4 (19.0%)	2 (18.2%)	14 (26.4%)	2 (7.1%)
Skin and subcutaneous tissue disorders						0
Rash	3 (9.4%)	0	3 (14.3%)	0	6 (11.3%)	0

manic episodes. The data provide evidence that lithium was effective in reducing manic symptoms in approximately one-half of these participants.

Lithium was superior to placebo in reducing manic symptoms in these patients, albeit with a delay of between-group separation. Whether the primary and secondary efficacy analyses would differ if this study was a longer clinical trial remains an empirical question that warrants further study. Ethical considerations during the design of the study precluded a longer clinical trial with one of the arms being placebo. The dropout rates during this clinical trial accentuate the challenges of performing a double-blind, placebo-controlled study in this population.

In addition to participant age, the study results are similar to those of a meta-analysis of lithium-controlled trials in adults.[12] The calculated mean standardized effect size was reported to be 0.40 with a range of 0.11 to 0.55. The clinical trial reported herein suggests that the efficacy of lithium in children is similar to that reported in adults and highlights that rigorous study of an older drug can improve the armamentarium of drugs used in the pediatric population. These study results add to the findings of the other large pediatric bipolar study, the National Institute of Mental Health–funded TEAM (Treatment of Early Age Mania) study, which compared treatment with lithium, divalproex, and risperidone in outpatients.[30] However, in that study, lithium and divalproex were each found to be less effective than risperidone.

Lithium was generally well tolerated in the present study. The adverse effect profile was consistent with what has been previously reported in adults. Of note, lithium was not associated with weight gain relative to placebo. This observation distinguishes lithium from the antipsychotic agents,[31–34] some of which have been shown to be effective in the acute treatment of manic and/or mixed states in this population but with a risk of substantial weight gain and metabolic derangements.

A potential limitation of the present study is that LOCF was used in the analyses. LOCF may bias an estimate of the treatment and underestimate variability of the estimated result. Sensitivity analyses have been performed by using mixed model repeated measures, which do not include imputed data for missing values and use all available YMRS scores at each visit. Results of both methods of analyses indicate the statistically significant superiority of lithium versus placebo. The mixed model repeated measures analyses showed significance only at the week 6 and week 8 time points.

The study does have some limitations. It was relatively brief, and BP-I is a chronic, recurrent condition; therefore, definitive conclusions about long-term efficacy cannot be made from these data. Another shortcoming of this research is that current scientific methods preclude the absolute certainty of the diagnosis of BP-I in this cohort. In addition, the study enrolled a relatively small sample. Therefore, uncommon adverse effects during acute treatment were likely not observed. The relatively modest sample size may also explain why between-group differences were not found on the secondary efficacy measures. In addition, sample size considerations limit the ability to perform analyses on subpopulations and extrapolation to a more general pediatric population.

CONCLUSIONS

Lithium exhibited efficacy in the acute treatment of pediatric BP-I. With the dosing regimen used, lithium was found to have a generally acceptable adverse effect profile. Although use of the sustained-release formulation of lithium may obviate vomiting, this question is empirical and has not yet been tested.

ABBREVIATIONS

AE: adverse event
BP-I: bipolar disorder I
CDRS-R: Children's Depression Rating Scale–Revised
CGAS: Children's Global Assessment Scale
CGI-I: Clinical Global Impression–Improvement
CGI-S: Clinical Global Impression–Severity
K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version
LOCF: last-observation-carried-forward
YMRS: Young Mania Rating Scale

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Article

Alterations in Skin Temperature and Sleep in the Fear of Harm Phenotype of Pediatric Bipolar Disorder

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Abstract: In children diagnosed with pediatric bipolar disorder (PBD), disturbances in the quality of sleep and wakefulness are prominent. A novel phenotype of PBD called Fear of Harm (FOH) associated with separation anxiety and aggressive obsessions is associated with sleep onset insomnia, parasomnias (nightmares, night-terrors, enuresis), REM sleep-related problems, and morning sleep inertia. Children with FOH often experience thermal discomfort (e.g., feeling hot, excessive sweating) in neutral ambient temperature conditions, as well as no discomfort during exposure to the extreme cold, and alternate noticeably between being excessively hot in the evening and cold in the morning. We hypothesized that these sleep- and temperature-related symptoms were overt symptoms of an impaired ability to dissipate heat, particularly in the evening hours near the time of sleep onset. We measured sleep/wake variables using actigraphy, and nocturnal skin temperature variables using thermal patches and a wireless device, and compared these data between children with PBD/FOH and a control sample of healthy children. The results are suggestive of a thermoregulatory dysfunction that is associated with sleep onset difficulties. Further, they are consistent with our hypothesis that alterations in neural circuitry common to thermoregulation and emotion regulation underlie affective and behavioral symptoms of the FOH phenotype.

Keywords: pediatric bipolar disorder; Fear of Harm; phenotype; thermoregulatory deficit; distal-proximal temperature gradient; sleep disturbance; parasomnias; sleep-onset latency; sleep diary; actigraphy

1. Introduction

Sleep disturbance is a common feature of mood disorders. In children diagnosed with pediatric bipolar disorder (PBD), problems with the quality of both sleep and wakefulness are prominent, and include bedtime refusal, sleep onset insomnia, parasomnias, morning sleep inertia, and daily bouts of both hyperactivity and hypoactivity [1–14]. An associated observation is that children with BD alternate noticeably between being excessively hot in the evening and cold in the morning [15,16]. Despite the pervasiveness of parental complaints and frequent clinical observations of sleep-related issues, there are few studies of sleep and rest/activity patterns in PBD, and data relating to temperature regulation in PBD are virtually non-existent. It is likely that methodological complexities of obtaining these data in children with psychiatric disorders are a primary reason for the lack of such studies. In addition, the very concept of childhood-onset bipolar disorder has been controversial, and only in the last decade have empirical investigations begun to characterize symptoms and examine potential etiologies of bipolar mood disorder in children [17,18].

A majority of children with bipolar disorder exhibit a subsyndromal course of illness. This has prompted many investigative groups to explore whether such a presentation is developmental or unique. Despite the ongoing debate, there has been a rapid increase in the rate of diagnoses of bipolar disorder in children (e.g., [19]). Concurrently, breakthroughs in neurology, neuroimaging, and genetics have called into question the existing conceptually-based psychiatric constructs altogether. New dimensional *versus* previous categorical research approaches which reflect these advances have made progress toward identifying dimensions of symptoms, or phenotypes, that are more likely to lead to evidence-based diagnosis and treatment. Such an example is a novel phenotype of PBD called Fear of Harm (FOH) [20–22].

The FOH phenotype includes symptoms that have not previously been associated with a nosological definition of bipolar disorder or other proposed childhood phenotypes of PBD [22]. However, many of these symptoms are recognized as co-morbid with the condition. In particular, separation anxiety, sleep/arousal disorders, parasomnias (night-terrors, enuresis) and REM sleep-related problems are primary features of the FOH phenotype. In addition, children with FOH often experience thermal discomfort (e.g., feeling hot, excessive sweating) in neutral ambient temperature conditions, as well as no discomfort during exposure to the extreme cold [23]. It is conceivable that an environmental signal expected to promote cold-defensive responses and lead an individual to seek warmth, to escape the cold, and to stimulate thermogenesis is not registered or not responded to, or the sensation/perception of change in cold ambient temperature is muted in these children, and therefore there is no aversive response generated by central thermoregulatory mechanisms.

An in-depth analysis of a large sample of children at risk for, or with a community diagnosis of, bipolar disorder, indicated that the population divides into approximate thirds of no-FOH, low-FOH,

and high-FOH [22]. Compared with children in the no or low FOH groups, children with high FOH have significantly higher indices of severity of mania and depression [22,23], and clearly fall within the domain of classical manic depression. Course of illness analysis has indicated that presence of the FOH trait associates with the most severe form of the illness, including early age of onset, frequent hospitalizations, significant social impairment, and school problems [22].

Children with the FOH phenotype, and bipolar disorder in general, also often experience sleep onset insomnia symptoms [1,6–9,11–13] that are typically reported in younger children as "bedtime refusal" or "difficulty settling at night". Older children self-report an inability to fall asleep, sometimes concurrent with racing thoughts and psychomotor agitation. In addition, both children and their parents complain of the children's severe morning lethargy and an inability to awaken spontaneously until later than similarly aged healthy children. We have hypothesized that these sleep- and temperature-related symptoms may be the overt symptoms of an impaired ability to dissipate heat, particularly in the evening hours near the time of sleep onset.

In an initial effort to confirm parental and clinical observations of these sleep and temperature problems, we examined rest/activity patterns using actigraphy, sleep parameters using parent-completed Sleep Diaries, and nocturnal skin temperature variables using a wireless temperature monitoring device, in children diagnosed with bipolar disorder, who met criteria for the FOH phenotype. These data were compared between children with FOH with a control sample of healthy children. With this approach we attempted to obtain high-quality objective data in a naturalistic setting, while circumventing some of the practical difficulties of studying sleep and temperature in children. The actigraphy and Sleep Diary data were utilized to obtain quantitative and qualitative information about sleep. Skin temperature data were utilized to examine relationships between a proxy measure of heat dissipation (*i.e.*, the distal-proximal gradient) and its relationship to sleep parameters, particularly latency to sleep onset.

We hypothesized that relative to the controls, children with PBD/FOH would have difficulty dissipating heat at bedtime, and further that this thermoregulatory symptom would be associated with longer latencies to sleep.

2. Experimental Section

2.1. Subjects

The study was reviewed and approved by the Weill Cornell Committee on Human Subjects in Research (Weill Cornell IRB). Potential subjects were recruited primarily via the research studies portal on the website of the Juvenile Bipolar Research Foundation. The aim of this initial screening methodology was to contact parents/caregivers of children who met criteria for the FOH phenotype, as described in detail in Papolos *et al.* (2009) [23], and controls with no psychiatric symptoms or history. Parents or caregivers completed the online Child Bipolar Questionnaire (CBQ [23]) and consented to being contacted if the responses indicated initial eligibility for the research study. Eligible subjects met the following criteria: CBQ total score >65, plus endorsed as being present almost always or always at least three of five sleep-related items on the CBQ, plus the CBQ item relating to rapid, abrupt mood swings, plus the CBQ item relating to thermal discomfort. Additional eligibility criteria (e.g., age

5–12 years old) were assessed via contact from the subject recruiter to the parent/caregiver respondent, and the study protocol was described. Eligible and interested adult/child teams were mailed study consent/assent forms. (Separate versions of assent forms were provided for children 5–7 years old *versus* 8–12 years old, as stipulated by the Weill Cornell IRB).

Following consent/assent, a diagnostic interview via telephone was conducted by a trained clinical rater using the K-SADS [24]. Diagnoses of DSM-IV Bipolar Disorder, or of no DSM-IV diagnoses for control subjects, were confirmed by expert consensus using information from the diagnostic interview and K-SADS.

Reported here are data from 16 children with PBD/FOH (9M, 7F; mean age = 8 ± 2 years, range 5–12 years). Mean age of onset of PBD was 4.25 years. All met criteria for FOH phenotype [19]. Control data are from 4 subjects (4M, mean age = 8 ± 1 years, range 7–9 years).

A study kit was provided to each adult/child subject team, and returned at the end of the protocol. The kit included a programmed Actiwatch (Respironics Minimitter, Inc., Bend, OR, USA), a programmed Vitalsense monitor with activated wireless dermal temperature patches (Respironics Minimitter, Bend, OR, USA), labeled Salivette tubes (Alpco Diagnostics, Inc., Wyndham, NH, USA) for saliva collection, and an instruction binder with 14 copies of a Sleep/Medication/Activity Diary (Diary).

2.2. Protocol

2.2.1. Diary

On each one-page Diary the adult/child team cooperated to complete questions with quantitative answers about the time the child got into bed the previous night, or started to fall asleep if not in bed (diary Bedtime), estimated Sleep Onset Latency (SOL), estimated Waketime (*i.e.*, awakening from sleep; WT), and time the child got out of bed in the morning (Risetime). Additional qualitative questions completed each morning included whether the child had experienced any long awakenings, nightmares, night terrors, or other parasomnias, got out of bed for any reason, or changed sleeping locations at any time during the night. The second portion of the Diary was completed each evening by the adult and included questions about any medications the child had taken during the day, with their administration time and dose, as well as questions to help adjudicate the Actiwatch data (e.g., periods of removal of the Actiwatch during the day, nap times). Adults/children were instructed to complete the portion of the Diary with questions about the previous night's sleep period in the morning within 2 h of the child's Risetime, and the portion with questions about the day's activities and medication regimen in the evening hours.

2.2.2. Nocturnal Skin Temperature

The dermal patches were to be placed on the child's (a) lower left calf (distal), and (b) subclavicle region (proximal) at least 1 h prior to anticipated bedtime on 3 nights to record overnight temperature. In order for the successful detection of the signal from dermal patches, the Vitalsense monitor needed to be within approximately 3 feet of each of the patches. While awake and out of bed, the child wore the monitor in a nylon waistpack. At bedtime, the monitor was placed near the child on a nightstand or in the bed next to the child. Although an attempt was made to record temperature for 3 consecutive

nights and the intervening days, logistical and comfort considerations resulted in revised instructions for the adult to remove the sensors in the morning 1 h after the child got out of bed. The dermal patches transmitted skin temperature (*T*sk) to the Vitalsense monitor at a 1-min sampling rate and transmitted ambient temperature readings when the patches were removed from the child's skin. Skin temperature readings from the time of placement on the skin until 4 h later (*i.e.*, incorporating bedtime and nocturnal sleep onset) were analyzed to obtain the absolute distal temperature, absolute proximal temperature, and distal-to-proximal gradient (DPG).

2.2.3. Actigraphy

A small wrist-worn Actiwatch-L (Respironics Minimitter, Bend, OR, USA) was programmed to obtain activity data at a 2-min sampling rate for up to 30 days. The child was to wear the Actiwatch continuously, except for periods when the water-resistant watch would remain submerged in water for an extended time (e.g., bathing, swimming).

2.2.4. Data Analysis

Diary data were summarized for each child individually and then by group (Control, FOH). Parameters included average BT, SOL, Time Spent Asleep, WT, RT, Sleep Period Duration from Bedtime to Risetime, and Sleep Efficiency (Time Spent Asleep/Sleep Period Duration). From the continuous Actiwatch data individual sleep periods were extracted for analysis, each constrained by the Diary-reported Bedtime and Risetime of the corresponding night. Each sleep period was analyzed via Actiware 5.0, applying a medium sensitivity algorithm to distinguish sleep from wake epochs, and to thus estimate actigraphy-derived Sleep Onset Latency (minutes from the clock time of Bedtime to 5 contiguous sleep epochs) and Sleep Efficiency (SE; # of sleep epochs during sleep period divided by total # of epochs during the sleep period).

2.2.5. DPG/DPG0

Usable temperature data was operationally defined as data from nights in which *T*sk from both distal and proximal sensors was recorded starting a minimum of 30 min prior to Bedtime and continued for at least 3 h after Bedtime. The proximal-minus-distal *T*sk difference was calculated for each minute for each night. The resulting curve was the DPG curve. DPG0° was defined for each night as the clock time at which the DPG curve first crossed 0°. The difference, or gradient, between proximal and distal skin temperature has been validated as a measure of heat dissipation, a thermoregulatory process in which heat is shunted from the body's core to its shell [25–29]. The distal-proximal gradient (DPG) has a temporal relationship to sleep onset in normal subjects, such that when the gradient approaches 0°, sleep onset is imminent [25–27,30–32]. This temporal relationship has been shown to be more than coincident; peripheral heat loss through skin of the extremities appears to be functionally related to, and permissive of sleep onset [25,26,31,32]. In populations with compromised thermoregulatory function, this temporal relationship has been shown to be disrupted, with sleep onset difficulties as one result [28,32–35]. Converging evidence for the functional role of heat dissipation in

sleep onset indicates that promoting heat dissipation in those with sleep onset difficulties facilitates sleep induction [26,29,34].

Sleep, actigraphy, and temperature parameters were compared between Control and FOH groups using *t*-tests, or Mann Whitney *U* tests. While the unit of analysis was a parameter from an individual night, degrees of freedom (when applicable) were based on the number of subjects from each group contributing to the analysis. Spearman rank-order correlations estimated the strength of relationships between variables, including between ordinal and continuous variables.

3. Results and Discussion

From the 16 FOH children, usable Diary and Actiwatch data were obtained from 92 nights *versus* 37 nights from the 4 Control children. Coincident, usable Diary, Actiwatch, and temperature data were obtained from 26 nights from 10 children in FOH *versus* 8 nights from 4 children in Control.

3.1. Sleep

Table 1 shows results of sleep-related parameters calculated from the Diary and Actiwatch. Neither Bedtime nor Risetime differed significantly between FOH and Control children, and thus sleep period duration did not differ between groups. However, sleep onset latency from both Diary and actigraphy was 2–3 times longer in FOH than Control groups. As calculated from Actiwatch data, SE did not differ between groups, but was relatively low for both groups, which may reflect (a) the sensitivity of the algorithm applied to determine wakefulness *versus* sleep (medium sensitivity was used); (b) (related to the algorithm sensitivity) the detection of restlessness during sleep in both groups of children; and/or (c) relatively poor sleep, on average, in both FOH and Control children. A recalculation of sleep parameters from Actiwatch data using a less sensitive algorithm (*i.e.*, higher threshold for determining wakefulness) increased the SE ratio equivalently in both groups.

Table 1. Sleep parameters in Controls and Children with Fear of Harm phenotype.

Sleep Parameter (Source)	Control	FOH
Bedtime (d)	21:04 ± 0:40	21:10 ± 1:01
Risetime (d)	06:32 ± 0:50	07:23 ± 1:04
Sleep Onset Latency (d)	9 ± 5 min	27 ± 20 min
Sleep Onset Latency (a)	8 ± 4 min	37 ± 38 min
Total Sleep Time (a)	7 h 36 min ± 41 min	8 h 07 min ± 1 h 17 min
Sleep Efficiency * (a)	85.7% ± 7.1%	87.0% ± 6.2%
Sleep Period Duration (d)	9 h 13 min ± 44 min	10 h 04 min ± 1 h 28 min
Parasomnias reported	0	8

Source: (a) = derived from actigraphy; (d) = from Diary. * Sleep Efficiency is the ratio of Total Sleep Time to the interval from Sleep Onset to Risetime.

3.2. Parasomnias

In the control group, there was not a single report of a parasomnia event on the Diary. In the FOH group, Diaries from 8/16 subjects indicated that the child had experienced at least one parasomnia

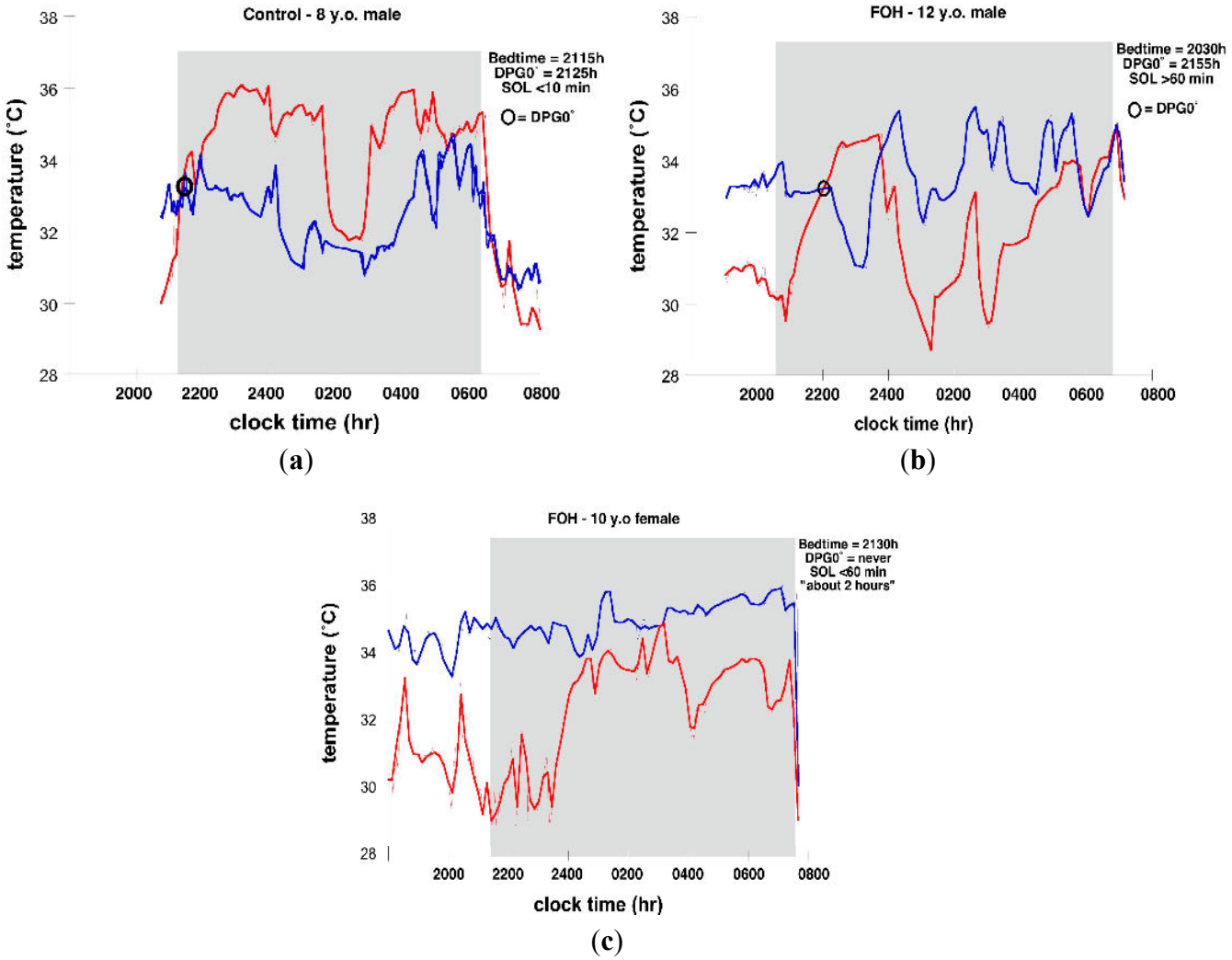
event on a given night. More than one unique parasomnia and more than one parasomnia event on multiple nights were reported in all but one of these eight children. The parasomnias reported were primarily nightmares, reported from six children, with two episodes of enuresis from the same child and three episodes of night terrors from three different children.

3.3. Skin Temperature and Sleep

The protocol indicated that skin temperature recording via the dermal patches and the Vitalsense monitor should begin at least 60 min prior to anticipated bedtime, or 1800 h, whichever was earlier. However, the average start time of skin temperature recording was 2012 h. This was, on a majority of nights, at least an hour prior to Bedtime.

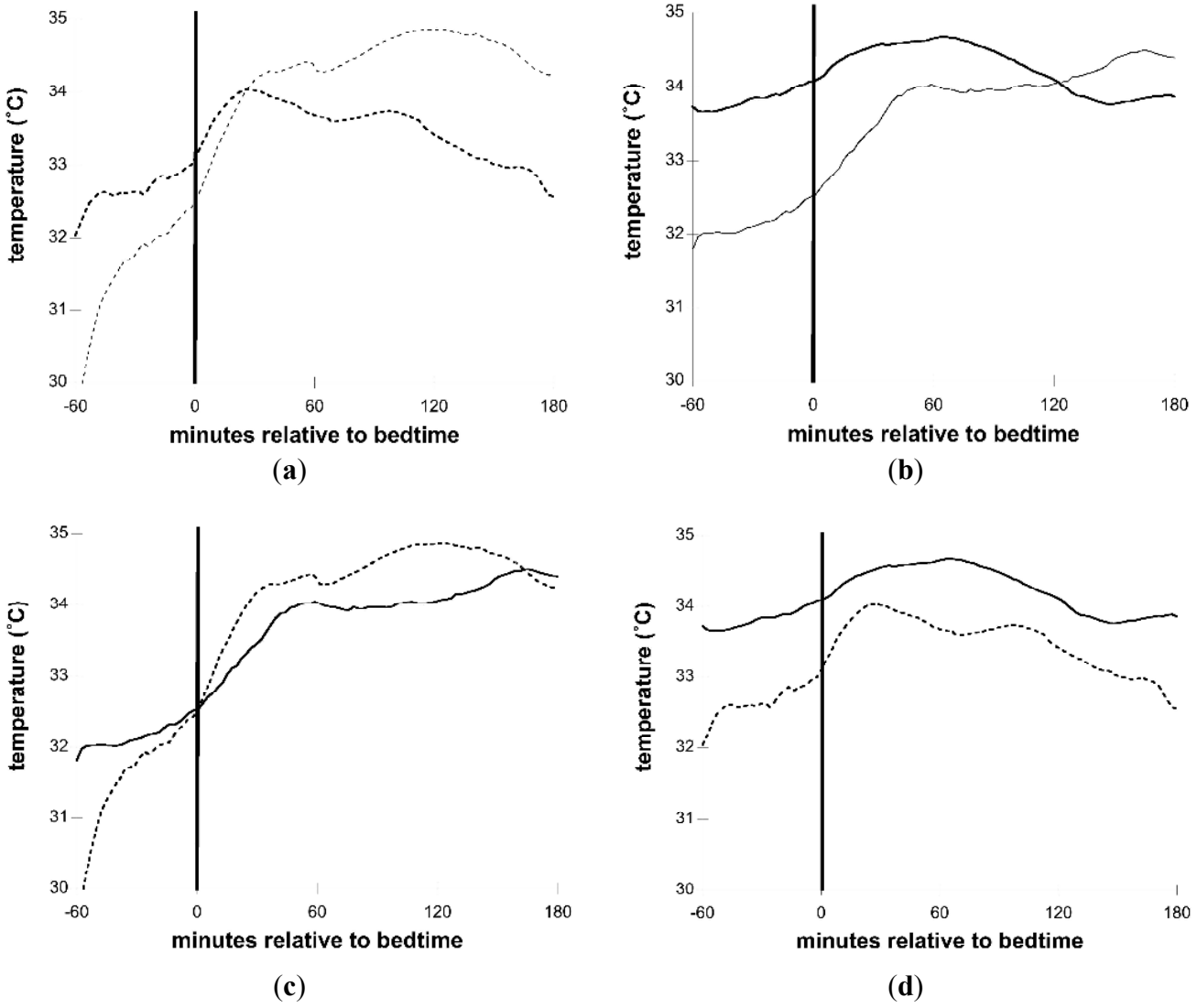
Figure 1a–c illustrates distal and proximal *T*sk and sleep timing on individual nights from 2 FOH and 1 Control. Figure 2a–d illustrate group mean *T*sk curves for the interval from 1 h (−60 min) before until 3 h (+180 min) after Bedtime.

Figure 1. Skin temperature and sleep timing in three children: (**a**) 8-Year old male Control (red line = distal temperature; blue line = proximal temperature); (**b**) 12-Year old male Fear of Harm (FOH) (red line = distal temperature; blue line = proximal temperature); (**c**) 10-Year old female FOH (red line = distal temperature; blue line = proximal temperature).



The average absolute distal *T*sk levels for the −45 min to +180 min interval surrounding Bedtime for all nights for Control and FOH groups did not differ. In particular, at Bedtime, the absolute distal *T*sk levels were essentially identical for both groups (control: 32.30°, FOH: 32.33°). However, proximal *T*sk averaged more than 1.2 °C higher in the FOH relative to Control group across the same interval. The largest magnitude of difference in absolute proximal *T*sk levels occurred in the interval from 45 min prior to Bedtime through 15 min after Bedtime. In the Control group, proximal *T*sk initially increased slightly at Bedtime, but as distal *T*sk increased substantially and quickly after Bedtime, proximal *T*sk started slowly decreasing, resulting in the DPG0° an average of 9 min after Bedtime.

Figure 2. Skin temperature relative to Bedtime. Smoothed curves from group averages of distal and proximal temperature from the 60 min before until 180 min after Bedtime; (**a**) Control (thin dotted line = distal; thick dotted line = proximal); (**b**) FOH (thin solid line = distal; thick solid line = proximal); (**c**) Control *vs*. FOH distal (dotted line = Control; solid line = FOH); (**d**) Control *vs.* FOH Proximal (dotted line = Control; solid line = FOH).



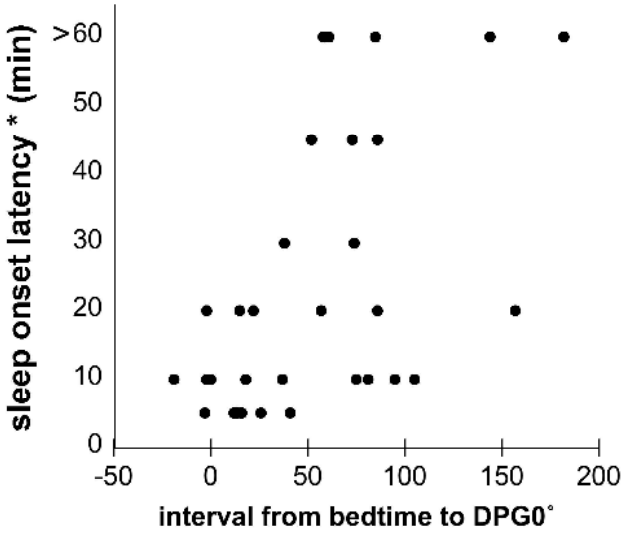
In FOH children, a different pattern of *T*sk around Bedtime was observed. On 4 nights from three different children in the FOH group, a DPG0° did not occur in the −60 min to +180 min analysis

interval. While distal *T*sk increased around Bedtime in a manner similar to Controls, proximal *T*sk remained higher before and in the 3 h after Bedtime in FOH children.

Due primarily to the lag in proximal *T*sk decrease, the time at which DPG0° occurred was significantly later in FOH children. Analyses of *T*sk relative to sleep revealed that DPG0° averaged 2114 h ± 40 min for Control and 2212 h ± 1 h 16 min for FOH groups, respectively ($t = 2.87$, $p < 0.05$). Similarly, there was a delay in the DPG0° relative to Bedtime in the FOH group, even though Bedtime did not differ between the groups. The interval from Bedtime to DPG0° averaged 11 min ± 15 min for Control children compared with 61 min ± 51 min for FOH children ($t = 3.21$, $p < 0.01$).

This lag between Bedtime and DPG0° was associated with a longer latency to sleep onset. SOL estimated by the Diary correlated significantly with the interval from Bedtime to DPG0° (SOL/BT-to-DPG0° interval: Spearman's rho = 0.48, $p < 0.05$; Figure 3). There was a similar trend for actigraphy-derived SOL (actigraphy-derived SOL/BT-to-DPG0° interval: Spearman's rho = 0.36, $p = 0.12$).

Figure 3. Relationship between interval from Bedtime to distal-proximal gradient of 0 degrees and sleep onset latency for individual nights with coincident Diary and skin temperature data from both Control and FOH subjects (Spearman's rho = 0.48; $p < 0.05$).



It was the common theme of parental and clinical reports that children with FOH exhibit signs and symptoms of altered thermoregulation that led to the current study. For example, children diagnosed with BD often have unusually reddened cheeks and ears, wear few layers of clothes in cold temperatures, and frequently complain of being hot even when others are comfortable. The anecdotal evidence for this phenomenon is quite widespread, and evidence for disturbed temperature regulation, particularly in the circadian domain, has been previously described in adults with affective illness [25–27], but to our knowledge, no systematic investigations of temperature perception or thermoregulation in PBD have been conducted.

An intimate association between sleep and body temperature has long been recognized, but a renewed interest in research on this topic has revealed that temperature regulation influences sleep to a greater degree than previously known. A growing body of evidence indicates that declines in core temperature and increases in peripheral heat loss may be functionally related to sleep initiation and

consolidation [28–35]. We and others have found that when the maximum rate of decline in core temperature (*i.e.*, the steepest slope) occurs prior, and in close proximity to bedtime, sleep onset latency is reduced, and slow wave sleep is increased [28,31]. An elegant series of studies by Krauchi and colleagues determined that peripheral heat loss via distal vasodilation, which drives the nocturnal decline in core temperature, is a permissive condition for sleep initiation [28–30]. In brief, they find that sleep onset occurs when the DPG approaches 0 degrees. The DPG0° was a better predictor of sleep onset than core body temperature, its rate of change, heart rate change, melatonin levels, or subjective ratings of sleepiness [28]. A complementary body of work by van Someren and colleagues has systematically demonstrated the role of skin temperature in sleepiness (e.g., [32,33]), and how manipulating the amount of heat dissipated via the skin can alter centrally-regulated vigilance levels and sleep propensity [34,35].

Some types of insomnia are associated with heat dissipation problems. Individuals with vasospastic syndrome, who have deficient vasodilation capacity, require twice as long to fall asleep as healthy controls [36]. Also, compromised capacity to lose heat from the periphery has been hypothesized to largely account for sleep maintenance insomnia in elderly individuals [37–39] and in women with menopausal hot flashes or night sweats during sleep [40]. It is conceivable that children with BD have thermoregulatory dysfunction that affects the capacity for heat dissipation and thereby interferes with the sleep initiation process. It is further possible that the neural mechanisms underlying the disruption in both thermoregulation and sleep regulation also modulate or mediate emotion dysregulation in these children.

4. Conclusions

The current data add to the emerging evidence for physiological and behavioral underpinnings of the FOH phenotype of pediatric bipolar disorder. Objective evidence of sleep disturbance, in the form of long sleep onset latencies, is in agreement with a large body of anecdotal, questionnaire, and empirical evidence for sleep problems in these children. Although neither Bedtime/Risetime, nor sleep period duration were obviously aberrant in the FOH children in this study, the average Diary-estimated sleep onset latency of greater than 30 min is comparable to that of sleep onset insomniacs.

It is necessary to note the numerous and varied difficulties with this in-home study, which limit interpretation of these data. As one result of these mostly logistical difficulties obtaining reliable diary, skin temperature, and sleep/wake data in children, the number of usable datasets (defined as having temperature on at least one night, and Actiwatch data for at least 7 nights) obtained were from a far smaller number of subjects than were enrolled in the study. Nonetheless, the clinical characteristics of these subjects (and Controls) are well-defined, the sample is well-characterized, and the information from the small sample is compelling.

The correlational nature of these results and the small sample size proscribe attributing directionality of effects among temperature, sleep, and emotion regulation disturbances. Nonetheless, the results are suggestive of a thermoregulatory dysfunction that is associated with sleep onset difficulties in children with a clear dysregulation of emotion as manifest in the Fear of Harm phenotype. They are consistent with our hypothesis that alterations in neural circuitry common to thermoregulation and emotion regulation, involving the orexin system, underlie affective and behavioral symptoms of the FOH

phenotype [22]. At a minimum, additional studies of thermoregulation in children with this psychiatric condition are warranted.

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Author Contributions

Patricia J. Murphy was responsible for coordinating study implementation and data collection, data management, analysis, interpretation, and initial drafts of the manuscript. Demitri Papolos was closely involved with analysis and interpretation of data as well as co-writing drafts of the manuscript. Mark G. Frei contributed to development of data processing and analysis strategies, interpretation, and manuscript preparation.

Conflicts of Interest

The authors declare no conflict of interest.

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Article

Thermoregulatory Fear of Harm Mood Disorder: In Depth Exploration of a Unique Juvenile-Onset Phenotype That Provides a Parsimonious Clinical Description of Certain Youths with Highly Comorbid Treatment Refractory Psychiatric Disorders

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ABSTRACT

Among aggressive youths with severe mood lability who frequently fail to benefit from mood stabilizers and antipsychotics there is a discrete subtype called 'Thermoregulatory Fear of Harm Mood Disorder' (FOH). This disorder is characterized by an underlying thermoregulatory deficit, a specific prodromal sequence and a unique constellation of symptoms. The underlying problem appears to be a deficit in thermoregulation resulting in excessive heat that manifests as thermal discomfort in neutral ambient temperatures and moderate to extreme cold tolerance, and produces REM sleep-related problems and parasomnias, such as night-terrors and hypnogogic hallucinations. Clinically, FOH is associated with the advent in childhood of frequent, recurrent, vivid nightmares with themes of pursuit and abandonment. The apparent psychological sequelae of exposure to this frightening imagery is fear sensitization and auto-traumatization. A developmental sequence of fear based defensive behaviors arises and includes obsessive bedtime rituals, fear of the dark, separation anxiety, contamination fears, hypervigilance, perfectionism, misperception of neutral stimuli as threatening, as well as reactive aggression in response to limit setting and perceived threat or loss. Ketamine, chosen as a potential treatment because of its effectiveness in reducing fear sensitization and dose-dependent lowering of body temperature in preclinical studies, has been associated with sustained

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improvement in otherwise refractory youths. We present a detailed description of this heritable disorder, link its clinical features to a potential disturbance in brain derived neurotropic factor (BDNF) and orexin, and indicate how ketamine rapidly affects BDNF through multiple mechanisms, to produce a dramatic beneficial response in youths with this disorder.

KEYWORDS: fear sensitization; juvenile bipolar disorder; aggression; ketamine; comorbidities

INTRODUCTION

This concept paper has three aims. The first is to further describe a novel clinical phenotype we call Thermoregulatory Fear of Harm Mood Disorder (FOH). The unique constellation of symptoms seen in FOH that are associated with fear sensitization can be frequently observed in some youths with early onset bipolar disorder [1,2]. These individuals experience intense fears related to abandonment, loss, injury and death, engage in aggressive behaviors directed toward self or others, undergo intense mood fluctuations, frequently require hospitalization and generally fail to respond to anxiolytics, antipsychotics, and mood stabilizers alone, but may experience sustained benefits from intranasal ketamine when combined with lithium salts. The second aim is to present a detailed neurobiological model that explains how a physiological abnormality—a deficit in thermoregulation—is both a critical etiological factor that initiates a prodromal symptom cascade, as well as a reliable marker for treatment response. Thirdly, we propose a molecular mechanism whereby a change in *Bdnf* gene expression, known to affect the development of fear sensitization and the establishment of a thermoregulatory set point, and alterations in orexin/hypocretin may underlie the development of this unique psychiatric phenotype. This understanding at the molecular level may also provide an explanation for the sustained effectiveness of the glutamate receptor antagonist, ketamine, in the treatment of this disorder.

CLINICAL PRESENTATION

Symptoms, Pathognomonic Features and Prodromal Sequence

FOH is a recently proposed clinical disorder that has been explored in seven published papers [1–7] and awaits independent validation. The modal FOH patient is a child between 6–12 years of age, who comes to clinical attention because of intermittent, rageful temper tantrums during which objects are broken and physical or verbal aggression is directed at self or others in response to separation from caretakers, unexpected changes in routine, perceived rejection or criticism, attempts to set limits or a parental “No” [1,2,4–7]. Clinical assessment reveals an

array of symptoms including affective lability with clear periods of sadness as well as a brief manic-like state characterized by increased goal-directed activity ("mission mode"), talkativeness and irritability if thwarted [1,2,4–7]. Comorbid symptoms of anxiety (separation anxiety, phobias with possible panic attacks), oppositional defiance, non-suicidal self-injury, violent obsession, inattention, impulsivity and features of post-traumatic stress disorder (PTSD) are present to varying degrees [1,2,4–7]. There are also some highly specific and potentially pathognomonic symptoms. The first is a thermoregulatory disturbance in which individuals feel uncomfortable (excessively hot, sweating) at neutral ambient temperatures and are moderate-to-extremely cold tolerant [2–4]. The second is a prominent sleep wake disorder with sleep onset insomnia, parasomnias (night-terrors, enuresis, bruxism, sleep-walking and sleep-talking), REM sleep-related problems (REM intrusions) and Nightmare Disorder (vivid, recurrent nightmares with themes of pursuit, death and abandonment) as well as morning sleep inertia [3,4,7]. The crucial features are the vivid nightmares and night terrors. Developmentally, a prodromal sequence of fear-based defensive behaviors arises and includes obsessive bedtime rituals, fearfulness of intruders, fear of the dark, separation anxiety, germ contamination fears, hypervigilence, misperception of neutral stimuli as threatening, and reactive aggression in response to limits, perceived threat or loss [2,4].

Auto-Traumatization

Our impression is that these individuals auto-traumatize to these terrifying nocturnal events and develop a posttraumatic reaction. A diagnosis of PTSD requires experiencing a Criterion A trauma defined as exposure to actual or threated death, serious injury, or sexual violence, which can be experienced, witnessed, or indirectly perceived (e.g., learning that the event occurred to a close relative or friend) [8]. Individuals with FOH repeatedly experience being severely injured, violated or killed in their nightmares, or experiencing doing these things to close family or friends [1,2,4,7], which we suspect may be quite traumatizing. In addition to experiencing trauma a DSM-5 diagnosis of PTSD requires at least 1 Criteria B and C and 2 Criteria D and E symptoms [8]. Individuals with FOH generally have: Criterion B intrusive symptoms consisting of emotional distress and physical reactivity to traumatic reminders; Criterion C avoidance symptoms, particularly attempts to avoid sleep; Criterion D negative alterations in cognition and mood, such as negative self-appraisal, shame, negative affect, feeling isolated and Criterion E alterations in arousal and reactivity including irritability and aggression, risky or destructive behavior, hypervigilance, heightened startle reactions, difficulty concentrating and difficulty sleeping [1,2,4–7]. Hence, a key component of FOH is the emergence during childhood or adolescence of an auto-traumatized variant of PTSD in addition to a

profound mood disorder, fear-based obsessions, aggressive behaviors, sleep disorder and thermoregulatory problems.

Impairment and Outcome

This is without doubt an extremely serious disorder. The child's symptoms typical increase to the point that they are no longer able to attend school because of their intense fears and have lost all or nearly all of their friends. Fifty-five percent of FOH youths in our recently reported sample had one or more psychiatric hospitalizations prior to successful treatment [4]. They received at various times one or more of the following diagnoses: major depression; bipolar disorder; separation anxiety disorder; simple phobias; social phobia; generalized anxiety disorder; disruptive mood dysregulation disorder; oppositional defiant disorder; nightmare disorder; ADHD and obsessive-compulsive disorder. Typically, they have been prescribed mood stabilizers (e.g., lamotrigine, lithium, oxcarbazepine, topiramate and valproate), atypical antipsychotics (e.g., aripiprazole, asenapine, clozapine, fluphenazine, olanzapine, quetiapine, risperidone and ziprasidone) and anxiolytics (e.g., clonazepam and lorazepam) with minimal benefit [4]. We have reported in both acute [6] and long-term [4] case series the clinically beneficial effects of intranasal ketamine in this population. After initiation and titration of intranasal ketamine they were often able to attend regular school, had ceased fighting with parents, were making new friends and were on a simpler drug regimen [4].

Diagnostic Criteria

Box 1 presents our latest version of a DSM-like set of diagnostic criteria for FOH intended primarily for clinicians who wish to identify individuals with this disorder in their patient population, and for researchers who wish to further study this proposed diagnosis. Criteria include: (A) the presence of a prominent mood disorder with episodic and abrupt transitions that fits within the broadest conceptualization of bipolar disorder [9]; (B) fear of physical harm with associated emotions and perceptions; (C) a characteristic disturbance in thermoregulation and heat dissipation; (D) a characteristic disturbance in sleep with nightmares and fear sensitization; and (E) reactive aggression directed towards self or others. The number of required symptoms within each category (and the number of required categories) should be taken as a guide that will likely be revised with further study, particularly as FOH may be better understood from a dimensional than categorical perspective [2]. Participants with FOH in prior studies [1–4,6] were diagnosed based on history of DSM-IIIR or DSM-IV bipolar disorder (bipolar I, bipolar II or bipolar NOS) and presence of aggressive obsessions on the Yale–Brown Obsessive Compulsive Scale (YBOCS) [10] (as captured in category B) and measures of extreme physical aggression towards self or others on the Overt Aggression Scale (OAS) [11], as

captured in category E. About 1/3 youths with pediatric bipolar disorder (PBD), or at high risk based on family history, had all, or nearly all, symptoms as originally conceptualized and 1/3 had none [11]. This suggests that many youths with PBD will have at least some symptoms of FOH. Further research is required to understand the prevalence and potential therapeutic implications of FOH symptoms in PBD in general, particularly alterations in thermoregulation and auto-traumatization which may be the most discriminatory features.

Box 1. Diagnostic criteria for thermoregulatory fear of harm mood disorder in DSM style format.

A–F are required for diagnosis and must be present most days for at least 6 months, without any symptom free periods that exceed 2 months in duration and cause functional impairment in one or more settings (e.g., significant behavioral problems at home but not necessarily in the school setting).

A. Mood Disorder. (Typically characterized by episodic and abrupt transitions in mood state accompanied by rapid alternations in levels of arousal, emotional excitability, sensory sensitivity, and motor activity).

1. Meets DSM-5 criteria for any form of bipolar disorder (bipolar I, bipolar II, mixed episodes, major depression with short duration mania, major depression with insufficient criteria hypomania, hypomania without major depression, cyclothymia). Manic, hypomanic and mixed episodes are defined by DSM-5 symptom criteria but not by DSM-5 duration criteria.

B. Fear of Harm. (Fear that physical harm will come to self or others; easily misperceives and experiences neutral stimuli such as tone of voice or facial expression as threatening; obsessive bedtime rituals; fear of the dark; fear of intruders; separation anxiety; contamination fears; hyper-vigilance).

Three (or more) of the following are required:

1. Obsessive fears that something awful may happen to self or significant others
2. Obsessive fears that they will harm themselves or others
3. Reacts with excessive anxiety and fearfulness in novel situations or with strangers
4. Reacts with excessive anxiety in situations involving separation
5. Is self-conscious and feels easily humiliated in social situations
6. Easily misjudges other people as threatening, intimidating or critical

C. Thermoregulatory Disturbance. (Experiences thermal discomfort such as feeling hot, or excessively sweating in neutral ambient temperature environments, as well as little or no discomfort during exposure to moderate or extreme cold, and alternates noticeably between being excessively hot in the evening and cold in the morning).

Two (or more) of the following are required:

1. Feels excessively warm/hot at bedtime or overheats during the night
2. Feels cold in the morning having felt hot at bedtime
3. Feels excessively warm during day in neutral temperatures
4. Has moderate to extreme cold tolerance (able to go out into the cold without a jacket)
5. Overheats or sweats profusely with exertion

Box 1. *Cont.*

D. Sleep Disorder. (Most specifically characterized by highly disturbing nightmares or night terrors resulting in fear of going to sleep and auto-traumatization).

Two (or more) of the following

Frequent night-terrors or nightmares – often containing images of gore and mutilation
Fear of going to sleep because of disturbing dreams
Hypnogogic hallucinations
Excessively restless sleep

(Note insomnia/hypersomnia and other parasomnias not included as they are often occur in mood disorders without FOH).

E. Aggression. (Territorial and reactive aggression in response to limit setting and perceived threat or loss including aggressive fight-based speech or actions or self-directed aggression such as head banging, cutting or scratching self, suicidal thoughts or actions).

Two (or more) of the following are required:

1. Excessively aggressive or controlling speech (critical, sarcastic, demanding, "bossy")
2. Excessive anger and oppositional/aggressive responses to situations that elicit frustration
3. Self-directed aggression (head-banging, skin-picking, cutting, suicidal ideations or actions)
4. Temper tantrums
5. Often threatens or breaks objects, slams doors, smashes walls

F. Symptoms are not due to a general medical condition (e.g. hypothyroidism). Criteria may overlap with symptomatology from other DSM classifications.

G. Family history of bipolar disorder. Lends further support to the diagnosis.

Research Domain Criteria (RDoC) were developed by NIMH to provide a means of understanding the nature of mental health and illness in terms of dysfunctions in specific psychological/neurobiological systems [12]. RDoC was not designed to serve as a diagnostic guide, nor to replace current diagnostic systems. However, we thought that it would be helpful for researchers if we delineated the RDoC systems, constructs and subconstructs that appear to be affected in youths with FOH. These are outlined in Table 1 and include nearly all systems, though the major alterations appear in the Arousal and Regulatory, Negative Valence and Social Processes Systems.

Table 1. RDoc Domains and Categories (in bold) that Appear to be Implicated in Thermoregulatory Fear of Harm Mood Disorder (FOH).

Domains	Categories
Negative Valence System	1. Frequent, inappropriate and sustained states of **Acute Threat ("Fear")** (e.g., in restaurants, school or at bedtime). 2. Characteristically in state of **Potential Threat ("Anxiety")** or **Sustained Threat** when not experiencing **Acute Threat**. 3. Periods free from **Threat** are rare and short-lived. 4. Episodes of extreme **Frustrative NonReward**–as manifest in temper tantrums and rages.

Table 1. *Cont.*

Domains	Categories
Positive Valence System	1. Basal state of low **Reward Responsiveness** and low **Reward Valuation**. 2. Occasional brief spontaneous periods of high **Reward Responsiveness** and high **Reward Valuation**.
	Cognitive System
	Occasional brief spontaneous periods of impaired **Cognitive Control** in which **Goal Selection** and **Response Selection** become fixated on a narrow set of goals and actions.
	Social Processes
	1. Disrupted **Affiliation and Attachment** characterized by overattachment to parental figure, deficient affiliation with others and social withdrawal; resulting in limiting and constrained friendships. 2. Impaired **Social Communication** in which **Reception of Facial and Non-Facial Communication** are misconstrued as threatening or disapproving. 3. Impaired **Perception and Understanding of Others** in which the **Actions** and **Mental State** of others are misconstrued as threatening or disapproving. 4. Impairment in P**erception and Understanding of Self** > **Self Knowledge** characterized by unshakable, highly negative or critical thoughts about self (abilities, self-worth).
Arousal and Regulatory Systems	1. In state of high **Arousal**, particularly when experiencing **Acute Threat.** 2. Oversensitivity to environmental stimuli producing state of high **Arousal**. 3. Disruption in **Circadian Regulation** of temperature / heat dissipation as manifest by feeling excessively warm at night and cold in the morning with moderate to extreme tolerance to cold and intolerance of heat. 4. Disruption in **Circadian Regulation** of temperature as manifest in deficient heat transfer from core to proximal extremities while endeavoring to fall asleep, resulting in delayed or absent DPG^0 during sleep initiation. 5. Prominent disturbance in **Sleep Wakefulness** as characterized by difficulty falling asleep, difficulty arising, frequent intense nightmares, REM intrusions and other parasomnias.
Sensorimotor Systems	Motor actions match **Negative** and **Positive Valence Systems** and **Arousal** states.

IDENTIFICATION OF THE PHENOTYPE

Heritability of Clinical Features in Youths with Bipolar Disorder

Thermoregulatory Fear of Harm Mood Disorder (FOH) emerged from an effort to identify the genetic associates of pediatric bipolar disorder (PBD) [5] using an endophenotype approach similar to Cheng *et al.* [13] and Faraone *et al.* [14]. The Child Bipolar Questionnaire (CBQ) [15], a 65 item, self-administered, parent report measure derived from Depue *et al.*'s [16] dimensional approach to the identification of adults at risk for bipolar disorder, was used to assess the range and severity of symptoms seen in a large sample of youths who had been given a community diagnosis of bipolar disorder or were at high risk for developing this disorder based on an enriched family history [5]. A factor analysis of the CBQ was conducted using N = 2795 children who screened positive for PBD on the CBQ. The resulting factors were used in a concordance analysis between N = 260 proband/sibling pairs and N = 260

proband/matched comparison pairs. Factors extracted included: fear of harm, depression, aggression, mania, sleep-cycle problems, anxiety and executive function deficits. Of the ten factors extracted from the CBQ the strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between proband/sibling *vs.* proband/comparison pairs, were for the Fear of Harm factor, that implicates this as an important heritable trait [5].

Fear of Harm Index

The CBQ was then used to further elucidate FOH in children with community diagnoses of PBD or at risk for the illness because of on enriched family history (*N* = 5335). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always and were diagnosed with all forms of PBD (e.g., BPI, BPII and BPNOS). This group was divided randomly into two groups, an exploratory group (*N* = 2668) and a hypothesis testing (study) group (*N* = 2666) [2]. A FOH Index was created using six items from the Yale–Brown Obsessive Compulsive Scale (YBOCS) and two items from the Overt Aggression Scale (OAS) [11]. The YBOCS items were measures of aggressive obsessions (*i.e.*, fear might harm self, fear might harm others, fear harm might come to self, fear harm will come to others—may be because of something the child did or did not do, fear of acting on unwanted impulses and fear they will be responsible for something else terrible happening). The OAS items were measures of extreme physical aggression (*i.e.*, mutilates self, causes deep cuts, bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth and attacks others causing severe physical injury). The score consisted of the number of YBOCS items rated by parents as occurring “often”, “very often” or “almost constantly” and number of OAS items rated 2 or higher. It was found that 1/3 met all criteria for the phenotype (FOH index ≥_7), 1/3 had no symptoms of FOH (FOH Index = 0), and 1/3 had symptom severity somewhere between these extremes. Compared to children with PBD who have no or low FOH, children with high FOH had significantly higher indices of severity of mania and depression and greater number of hospitalizations. The groups did not differ in age of onset, age at first diagnosis or age at first hospitalization. FOH therefore constitutes a large proportion of children diagnosed with cycling mood disorders who are among those that demonstrate the most significant levels of pathology.

THERMOREGULATION AND SLEEP

FOH and Temperature Sensitivity

In addition to the CBQ items that defined behaviors linked to FOH, a cluster of symptoms were identified during clinical evaluation that are highly suggestive of a disturbance in temperature sensitivity and regulation. Patients with FOH were noted to experience thermal

discomfort (e.g., feeling hot, excessive sweating in neutral ambient temperatures or on exercise) but no discomfort during exposure to moderate or extreme cold. Further, they would noticeably alternate between being excessively hot in the evening and cold in the morning. Individuals with FOH typically wear few layers of clothes in cold temperatures, and frequently complain of being hot even when others are comfortable. Overheating and the sequelae of peripheral vasodilation; facial flushing, deep red, warm pinnae of the ears and dark circles under the eyes often accompany “affective storms”, panic or aggressive behaviors in response to stressors, which has been labeled as psychogenic or emotional hyperthermia [17].

This unique group of seemingly independent traits, associated with an aberrant response to a perceived threat and a disturbance in thermoregulation, are considered central to the clinical presentation of the phenotype. We believe that the temperature-related symptoms associated with FOH are overt manifestations of an impaired ability to dissipate heat, particularly in the evening hours near the time of sleep onset and thereby interfere with the circadian sleep initiation process as well as transitions between sleep arousal states that typically have a 1–2 h ultradian periodicity [3].

Brain Temperature Homeostasis

This makes sense as temperature has a critical impact on sleep as well as on a vast array of other brain functions. The homeostatic imperative to maintain core body temperature has been well known since the time of Claude Bernard and Walter B. Cannon. However, there is increasing awareness that there is also a more specific homeostatic challenge of maintaining brain temperature as CNS function can be dramatically affected by slight shifts in temperature and the brain is more vulnerable to hyperthermic damage than other organs. Further, the brain, like a computer CPU, has a tremendous potential to run hot and overheat. Brain cells utilize 300–2500 times more energy than the average body cell [18] causing the brain to consume 20% and 25% of total body oxygen and glucose though it only accounts for about 2% of body weight [19]. Intense heat production is an essential feature of brain metabolic activity as all energy used for brain metabolism is eventually transformed into heat [18].

In general, brain regions at rest are about 1 °C warmer than arterial blood, though different brain regions maintain different specific temperatures [18,19]. Sensory stimuli, such as tail pinch or change in cage placement of rats, produces a very rapid ~1–2 °C rise in the temperature of specific brain regions and the subsequent increase in blood flow may play an important role in cooling as well as increasing delivery of oxygen and glucose [18]. Further, natural occurring fluctuations in brain temperature affect membrane potentials, burst firing rates, and the release and reuptake of neurotransmitters [18]. Temperature sensitive neurons, critical for thermoregulation, were

initially identified as a discrete population of cells in the preoptic/anterior hypothalamus (POA). They have since been identified in visual, motor and somatosensory cortex, hippocampus, brain stem and substantia nigra [18]. The medial thalamus and suprachiasmatic nucleus actual have a greater percentage of thermosensitive neurons than the POA [18]. A wide range of sensitivity is achieved through the participation of distinct types of channels that are each sensitive to narrow yet overlapping ranges in temperature [20,21]. A great deal more needs to be learned regarding brain processes responsible for brain temperature homeostasis and the clinical consequences that might ensue from abnormalities in heat dissipation from the brain.

Sleep and Body Temperature

The relationship between sleep and core body temperature however, is reasonably well understood. Sleep is governed by both a circadian process, most clearly reflected in the ~24-h rhythms in core body temperature and melatonin release, and a homeostatic process in which sleep debt progressively accumulates during wakefulness and is paid down by time spent in restorative slow wave sleep (SWS) [22]. Core body temperature decreases during the normal sleep onset period in humans as part of the underlying circadian rhythm and sleep further facilitates this reduction. The primary mechanism driving the reduction in core body temperature is increased blood flow to the skin, which is rich in arteriovenous anastomoses that play a critical role in thermoregulation [23]. These anastomoses open when noradrenergic vasoconstrictor tone declines, shunting blood from arterioles directly into the venous plexuses of the limbs [23], promoting greater inflow of heated blood from the core and facilitating heat loss to the environment through the skin surface [23,24]. This selective vasodilation of distal skin regions promotes the rapid onset of sleep and is strongly associated with melatonin secretion [24]. After sleep onset, core temperature continues to gradually decline while distal and proximal skin temperature remain elevated [24]. Higher measures of skin temperature are associated with increased sleep efficiency and time spent in SWS [24].

Homeothermic animals need to thermoregulate during sleep but capacity to do so varies by sleep stage. Shivering during sleep, as a defense against cold, is confined to stages 1 and 2. Sweat rate and heat dissipation are maximal during SWS. REM sleep is most significantly influenced by ambient temperature but during this stage thermosensitivity is markedly reduced and there is a delayed onset of sweating, decreased sweat rate, diminished evaporative heat loss and reduce heat tolerance [24]. To compound matters brain activity during REM is metabolically demanding. Previously known as paradoxical sleep, REM is characterized by rapid eye movements, cortical activation resembling wakefulness, vivid dreaming and skeletal muscle paralysis (atonia) [25]. Playing a central role in REM is the subcoeruleus nucleus

(part of the locus coeruleus/subcoeruleus complex), which produces REM paralysis through glutamineric connections to neurons in the ventromedial medulla and spinal cord that inhibit motor neurons through the combined action of GABA and glycine [25]. This sleep paralysis is critical as otherwise REM would be accompanied by vocal outbursts and violent arm and leg movements as seen in REM behavior disorder. Hence, both brain and core body temperature increase during REM and can pose a hyperthermic challenge if heat is not adequately dissipated. Conversely, core body and brain temperature fall to their lowest levels during SWS.

Body Temperature and Waking

Waking at normal times occurs in conjunction with rising core body temperature and falling peripheral temperature [26]. Two ascending pathways stimulate wake maintenance. One is a cholinergic pathway from the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei to the thalamus that activates thalamic relay neurons crucial for information transmission to the cortex [22]. These cells are active during waking and REM sleep and much less active during NREM. The second branch originates from monoaminergic cell groups in the locus coeruleus (LC), dorsal and medial raphe, ventral periaqueductal grey (vPG) and tuberomammillary (TM) neurons that provide noradrenergic, serotonergic, dopaminergic and histaminergic projections to the lateral hypothalamus, basal forebrain and throughout the cerebral cortex. These neurons are most active during waking, less activity during NREM sleep and are silent during REM [22]. The cell groups involved in wakefulness are reciprocally interconnected with the ventrolateral preoptic area which is primarily active during sleep and releases the inhibitory neurotransmitters galanin and GABA. Together these regions function as a ‘flip-flop’ switch toggling between sleep and wakefulness. This type of self-reinforcing loop produces relatively abrupt transitions between sleep and wakefulness but is inherently unstable [22]. Orexin projections from the hypothalamus with prominent connections to LC, raphe, vPG and TM promote wakefulness and stabilize the system by orchestrating the interaction between the various cell body regions involved in wakefulness [27]. Loss of orexin neurons in narcolepsy result in unstable shifts between wakefulness and sleep as well as bouts of cataplexy that stem from the intrusion of the REM sleep paralysis mechanism into wakefulness [25].

One might assume that alertness would be optimal shortly after awakening due to diminished sleep debt. That however is not the case as there is a significant degree of sleep inertia following waking that persists from minutes to hours. Interestingly, the decline in subjective sleepiness correlates very strongly with the rate at which the extremities cool and heat transfers from the periphery to the core in a process that mirrors the shift in temperature during sleep initiation [26].

Impaired Regulation of Nocturnal Temperature and Sleep in FOH

The presence of a thermoregulatory disturbance was confirmed in children with FOH via thermal skin patches placed on the child's lower left calf (distal) and subclavicle region (proximal) prior to and following sleep onset, which was assessed using actigraphs [3]. The key metric was the distal-to-proximal (DPG) thermal gradient defined as distal-minus-proximal temperature. This gradient has been validated as a measure of heat dissipation and it is well-known that distal temperature is lower than proximal temperature prior to sleep, that distal temperature rises and proximal temperature falls and that distal temperature generally exceeds proximal temperature until shortly before awakening. Interestingly, the point where proximal and distal temperatures meet and cross over (DPG^0) is highly coincident with sleep onset and plays an important permissive role in sleep initiation and awakening [28–31]. Proximal temperatures in children with FOH tended to run high throughout much of the night, delaying the onset of DPG^0 by nearly an hour and in some children with FOH DPG^0 failed to occur at any time [3]. In short, children with FOH appear to have a problem dissipating heat during the night and this disturbance was associated with delayed sleep onset, and serves as a risk factor for REM intrusions, nightmares, parasomnias and morning sleep inertia. We consider this thermoregulatory deficit a potential biomarker for FOH with possible causal implications.

These findings are consistent with our hypothesis that alterations in neural processes that underlie thermal regulation sets the stage for the development of sleep disorders, fear sensitization and poor modulation of aggression and other survival-based behaviors that are the manifest phenotypic features of FOH. Disturbances in all of these functions may be linked to a compromised orexin system that no longer provides appropriate regulation of the expression of these behaviors, nor smoothly executes survival based homeostatic functions [32]. Indeed, many of the aberrant behaviors seen in youths with FOH, for example separation anxiety and fear based aggressive responses to perceived threat, are best understood as responses to existential threat. Individuals with these phenotypic features appear to have a very similar pattern of response to psychopharmacological treatments, suggesting that this is a relatively homogeneous disorder with a common molecular basis.

FOH AND THERAPEUTIC RESPONSE

First Line Treatment *versus* Ketamine

Although FOH was initially recognized as a severe variant of juvenile onset bipolar disorder it became clear that individuals fitting this clinical description rarely experienced a meaningful clinical response to first-line treatments including atypical antipsychotics and mood stabilizers. Ketamine was selected as a tertiary treatment for these

severely ill and refractory youths based on success in adults with refractory mood disorders [33] and because of its effectiveness in reducing fear sensitization and dose-dependent lowering of body temperature in preclinical studies [34,35]. Remarkably, almost all experience a robust and sustained clinical response to intranasal ketamine administered approximately every 3 days. Indeed, we recently reported in a detailed assessment of individuals receiving extended treatment with intranasal ketamine for FOH, that these individuals were currently taking an average of 3 psychotropic medications prior to ketamine [4]. Overall, 80% were taking one or more atypical antipsychotics, 60% mood stabilizers, 29% antidepressants and 17% anxiolytics. Despite these treatments, they were seen as severely ill (Clinical Global Impression = 5.7 ± 0.7), with 10 of 48 patients rated as "amongst the most severely ill" by at least one of the two raters, and 53% had one or more psychiatric hospitalization prior to initiation of ketamine. Following ketamine, 21% were rated as very much improved and 67% were rated as much improved, with no subsequent hospitalizations over a more than 2 year follow up period [4].

To date we have restricted treatment with intranasal ketamine to youths with clear features of FOH and do not know how efficacious ketamine would be in refractory youths with bipolar disorder but without FOH. Overall, there is a pressing need for randomized, double-blind, placebo-controlled trials of ketamine in refractory PBD both with and without FOH.

It is important to note that the effects of ketamine were holistic and not limited to effects on mood. Indeed, an almost immediate effect of intranasal ketamine is to foster heat dissipation and patients often notice facial flushing, reddening and warming sensation in the pinna of the ears, and that the soles of their feet become quite warm during treatment. Effectively treated individuals typically lose much of their cold tolerance and the return of heat sensitivity and cold tolerance over the next few days heralds their need to receive another ketamine treatment in order to maintain benefits. Overall, pre-post differences in ratings were strongest for the factor that included the core FOH phenotypic features [4]. Hence, understanding the mechanism of action of ketamine may provide insight into the pathophysiology of FOH.

Direct Effects of Ketamine

Initial reports of a rapid and sustained antidepressant effect of ketamine, and subsequent studies showing its benefits in treatment refractory depression, anxiety, bipolar disorder, PTSD and suicidality [33,36–39], has stimulated a great deal of interest in the potential mechanism of action. Briefly, ketamine is a 50–50 racemic mixture of *R*- and *S*- optical enantiomers that act as non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists. The simplest theory is that ketamine works through direct NMDA receptor inhibition. Interestingly,

while ketamine would be expected to block excitatory glutamatergic neurotransmission via NMDA inhibition, it actually increases prefrontal cortical activity in healthy volunteers; likely due to a preferential inhibition of NMDA receptors located on GABAergic interneurons leading to a disinhibition of pyramidal neurons and enhanced glutamatergic firing [40]. In addition, ketamine blocks extra-synaptic NMDA receptors which are tonically activated by low levels of ambient glutamate [40] and it inhibits NMDA receptor-dependent burst firing activity of the lateral habenula, which is associated with depressive symptomatology [41]. However, while these actions may contribute to ketamine's antidepressant effects it appears that these are not the primary mechanism of action. We know this, in part, because other NMDA channel-blocking antagonists do not provide antidepressant effects of comparable magnitude, immediacy or duration [40]. Similarly, there is reasonable evidence that the R-enantiomer of ketamine has a superior and longer lasting antidepressant effect then the *S*-enantiomer, though the later has a 4-fold higher affinity for the NMDA receptor [40]. Further, deuteration of ketamine at the C-6 position, which does not affect NMDA receptor binding, but does inhibit conversion to (2*S*,6*S*;2*R*,6*R*)-hydroxynorketamine (HNK), blocks its antidepressant effects in animal models, suggesting that this metabolite is an essential component. Consistent with this finding is the observation that (2*R*,6*R*)-HNK is a more effective antidepressant than (2*S*,6*S*)-HNK, though the *R* enantiomer does not appear to have any effect on NMDA receptors at therapeutic doses [40]. Rather enantiomers of HNK appear to facilitate signaling through the α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutaminergic receptor, which are the primary receptors responsible for the transduction of fast synaptic neurotransmission in the brain [40].

Downstream Effects of Ketamine on Brain Derived Neurotrophic Factor

Although ketamine and its HNK metabolite have a multitude of direct effects at least four of these exert convergent downstream effects on brain derived neurotrophic factor (BDNF). The disinhibition of glutamate release through ketamine's effect on GABAergic interneurons stimulates post-synaptic AMPA receptors that are also facilitated by (2*S*,6*S*;2*R*,6*R*)-HNK resulting in enhanced release of BDNF [40]. Further, ketamine inhibition of extrasynaptic NMDA receptors, which are tonically activated by low levels of ambient glutamate, serves to disinhibit phorphorylation of eukaryotic elongation factor 2 kinase (eEF2K) resulting in an increase in protein translation in general and BDNF translation in particular [40]. Similarly, (2*R*,6*R*)-HNK also suppresses eEF2K phosphorylation and increases BDNF translation through a non-NMDA mediated mechanism [40]. The net result is that within minutes ketamine produces a marked and sustained increase in BDNF levels. Antidepressants also produce an increase in BDNF but only after several

weeks of treatment. Blocking the effects of ketamine on BDNF, or the downstream molecular effects of BDNF, blocks antidepressant response to ketamine in animal models [40]. Hence, this is likely a key effect of ketamine and leads in turn to the question regarding the relationship between BDNF and the phenotypic features of FOH.

BRAIN DERIVED NEUROTROPHIC FACTOR AND FOH

Function and Structure of BDNF

BDNF is a critically important protein that is synthesized and released by neurons in the brain and cells in the periphery. It exerts a vast array of effects that depend on location and stage of development. During development BDNF supports neuronal survival, growth and differentiation while promoting connectivity, neuroplasticity, neurogenesis as well as synapse, spine and dendrite formation in the mature brain. BDNF acts within minutes to enhance glutamatergic and reduce GABAergic synaptic transmission in CNS neurons [42]. Chronic exposure to BDNF enhances the formation and functional maturation of glutamatergic and GABAergic synapses [42] and has widespread effects on the serotonin systems [43,44]. It also plays a critical role in cycling of synaptic vesicles in rapidly firing neurons and is a crucial mediator of long-term potentiation (LTP) in multiple brain regions [42].

The human *Bdnf* gene has a complex structure consisting of 11 exons in the 5' end and nine promoters [45,46]. The coding sequence resides in exon 9, with eight upstream promoters regulating regional and cell-type-specific expression [46,47]. Each of the different *Bdnf* transcripts encode the exact same BDNF protein [45,46]. However, the selective expression of distinct *Bdnf* transcripts, that are specific to various tissues or cell types and responsive to different stimuli, explains how BDNF can effectively mediate such a wide array of behavioral and molecular functions [44].

As indicated above FOH is characterized by a deficit in thermoregulation, sleep disturbance, extensive periods of depression and brief periods of mania, intense fear-based obsessions, aggression towards self and others and characteristic features of PTSD. Many youths with FOH also experience carbohydrate craving. There is good support for BDNF playing a role in all of these aspects of the disorder.

BDNF and Thermoregulation

Translational studies indicate that BDNF is involved in two key aspects of thermoregulation. First, BDNF in the anterior hypothalamus has been reported to play an essential role during a critical developmental phase in the fine-tuning of a thermal-response set point in chickens [48]. Antisense attenuation of *Bdnf* in this region at this critical stage produces an enduring deficit in thermoregulatory capacity [48]. The critical step involves the epigenetic methylation and histone

modification of *Bdnf* gene promoters in the hypothalamus [49,50]. Presumably specific epigenetic modifications to *Bdnf* promoters during this critical period serve to regulate the emerging balance between warm and cold sensitive neurons in this region [48]. Second, these warm-sensitive neurons (WSNs) within the mammalian preoptic hypothalamus function to orchestrate the homeostatic response to heat [51] as their optogenetic excitation triggers rapid hypothermia, mediated by reciprocal changes in heat production and heat dissipation, as well as dramatic cold-seeking behavior [51]. BDNF likely plays an import role in their function as these neurons are molecularly defined by their co-expression of BDNF and pituitary adenylate cyclase-activating polypeptide (PACAP) [51].

BDNF and Sleep

Both clinical and translational studies show that BDNF plays a crucial role in the homeostatic regulation of REM and non-REM (NREM) slow-wave sleep (SWS). First, translational studies show that the homeostatic increase in sleep pressure for restorative SWS that builds during wakefulness is further moderated by the amount of exploratory behavior and cortical activation that occurs during this time, and that this is mediated by the degree of cortical BDNF expression [52–54]. More specifically it appears that activity-dependent BDNF expression increases sleep pressure by acting through tropomyosin receptor kinase B (TrkB) receptors on a subset of cortical and hippocampal GABAergic interneurons that express the neuropeptide cortistatin, which plays a critical role in regulating cortical inhibitory balance and degree of SWS activity [55,56]. Mice in which TrkB was selectively deleted from cortistatin-expressing interneurons sleep less and due to insufficient cortical inhibition become hyperactive and develop spontaneous seizures [56].

Second, translational studies indicate that BDNF also plays an essential role in the homeostatic regulation of REM sleep through a similar mechanism. Selective REM deprivation leads to an increase in BDNF protein expression in the pedunculopontine tegmentum (PPT) and the subcoeruleus nucleus (SubC) that regulate REM sleep, but not in the medial preoptic area, which regulates NREM sleep [57]. The increase in REM rebound following REM deprivation requires BDNF stimulation of TrkB receptors [58,59]. More detailed molecular analysis reveals that BDNF activation of TrkB receptors promotes extracellular-signal-regulated kinase 1 and 2 (ERK1/2) activity in cholinergic neurons within the PPT which, in turn, leads to the transcription of the *Bdnf* gene [60]. Pharmacological inhibition of s1/2 activation in the PPT prevents REM rebound and suppresses BDNF expression [60]. Orexin, in turn, serves as the master regulator of sleep/wakefulness states.

These findings are supported by clinical studies. In particular a very recent study by Deuschle *et al.* [61] measured morning serum BDNF levels followed by sleep polysomnography in a significant number of

participants with either primary insomnia, restless legs syndrome, idiopathic hypersomnia or narcolepsy as well as healthy controls. Across all disorders low BDNF levels were associated with a low percentage of SWS and REM sleep [61] consistent with translational studies indicating the importance of BDNF in generating the homeostatic drive for SWS and REM. Conversely, full or partial sleep deprivation, which increases sleep pressure and has been reported in several studies to produce a rapid reduction in depressive symptoms, leads to a rapid increase in BDNF levels [62]. This is highly consistent with preclinical findings and indicates that the rapid antidepressant effect of sleep deprivation and the rapid antidepressant effect of ketamine are both mediated by increasing levels of BDNF [62].

BDNF and Mood Disorders

There is strong clinical as well as translational support for an important role of BDNF in both depression and bipolar disorder [63]. First, as reviewed above there is compelling preclinical support for BDNF and its primary receptor TrkB as essential components in the mechanism of antidepressant action of ketamine [40] as well as in the mechanism of action of traditional antidepressants [64,65], electroconvulsive therapy [64,65], sleep deprivation [62] and exercise [66]. Similarly, genetic manipulations of the BDNF/ERK kinase pathway alters affective-like behaviors in mice in multiple ways, with most changes consistent with manic-like behavior [67]. Second, there is good evidence that peripheral BDNF levels are reduced in patient with major depression, though this may be moderated by severity and history of abuse or neglect [68–70]. Similarly, there is good evidence for reduced peripheral BDNF levels during depressed, manic and mixed phases of bipolar disorder [71–74] though this also may be moderated by degree of exposure to traumatic events [75]. More definitively, there is also evidence for reduced BDNF and TrkB mRNA expression in specific brain regions of post-mortem samples from individuals who had unipolar and bipolar disorders [76–78].

Pandey *et al.* [79] studied this association in PBD and found decreased levels of BDNF in platelets and decreased BDNF expression in lymphocytes in N = 26 unmedicated youths with PBD versus N = 21 controls. Moreover, BDNF measures increased to near normal levels after 8-weeks of treatment (N = 19). On the other hand, more recent studies have not found differences in BDNF serum levels between PBD and controls [80–82] nor an association between BDNF levels and symptoms of mania or depression [83]. These studies though did report associations between BDNF in serum and inflammatory markers [83], amygdala volume [81], risk factors for cardiovascular disease and measures of executive function [82]. They do not however, refute Pandey *et al.* [79] as they measured BDNF in serum versus lymphocytes and participants in these latter studies could be euthymic or medicated.

What is less consistent in clinical studies is the relationship between BDNF levels and clinical response. Some studies have reported a significant rise in BDNF levels with successful treatment [79,84] but other studies have not [85] or found no relationship between degree of rise and clinical response [86]. There are also several inconsistent reports regarding the relationship between the Val66Met functional polymorphism of BDNF and risk for mood disorders or prediction of antidepressant response [87–97]. It seems likely, at this point, that reduced BDNF levels in individuals with mood disorders does not generally arise from a specific polymorphism but may stem from genotype dependent environmental effects (particularly childhood maltreatment) leading to epigenetic modifications to promoters regulating different slice variants of *Bdnf* [98–110]. A key question in FOH is whether the potentially auto-traumatizing effect of frequent intensely disturbing nightmares acts as a form of childhood adversity that results in new or additional epigenetic alterations to the *Bdnf* gene.

BDNF and Fear

Fearful obsessions and defensive fear-based behaviors are hallmarks of this disorder. Both the formation and the extinction of fear memories requires *Bdnf* gene expression and activation of its high-affinity TrkB receptor [111,112]. FOH may be similar to PTSD in that the formation of fear based emotional memories appears to be intact but the ability to extinguish fear memories is severely impaired [111,113]. An overall defect in BDNF expression would affect consolidation as well as extinction suggesting that FOH and PTSD are associated with more circumscribed alterations in BDNF signaling.

Briefly, there are three key components to the fear circuit [112,114,115]. The first is the amygdala, particularly the basolateral nucleus, central nucleus and intercalated cells which together serve as the fear acquisition and expression hub. The second is the prelimbic and infralimbic subdivisions of the medial prefrontal cortex, which are respectively involved in the expression and extinction of fear memories. The third is the hippocampus which modulates these prefrontal regions and helps provide contextual information [112,114–116]. The prelimbic subdivision promotes fear by activating the basolateral nucleus, which stores fear-based associations, and has excitatory projections to the central nucleus. In contrast, the infralimbic portions projects to the intercalated cells and lateral division of the central nucleus, which contain GABAergic neurons that inhibit the output neurons of central nucleus [112,114,115]. There are also reciprocal connections between the basolateral nucleus and prelimbic cortex that become active during states of high fear and between basolateral nucleus and infralimbic cortex that are active during extinction [112,117]. Coordinated electrophysiological oscillations and neuronal synchrony facilitate communication between these regions and regulates synaptic plasticity.

States of high fear and anxiety are associated with increased theta power and synchrony between hippocampus, prefrontal cortex and amygdala, whereas extinction is characterized by decrease in phase synchrony and after successful extinction, with shift in directionality so that prefrontal theta oscillations now 'lead' amygdala theta oscillation [118,119].

BDNF signaling and regulation of synaptic plasticity are critically involved in all components of the fear circuit. Behavior deficits from impaired BDNF signaling depend upon the brain regions affected [112]. Decreasing BDNF signaling in the amygdala significantly impacts fear learning and consolidation [112,120–122] as does a deficit in prelimbic BDNF [123]. In contrast, diminished BDNF signaling in HPC or infralimbic cortex is associated with impairments in fear extinction [124,125].

Specific polymorphisms in the *Bdnf* gene can also lead to a selective deficit in fear extinction. For example, females are twice as likely to develop PTSD as males and female mice are more resistant than males to fear extinction. This appears to be due to increased DNA methylation of *Bdnf* exon IV and a concomitant decrease in mRNA expression within the medial prefrontal cortex [113]. Similarly, *Bdnf-e4* mice, in which the activity-dependent promoter in exon IV is disrupted, have impaired fear extinction and decreased hippocampal–medial PFC theta phase synchrony during extinction learning [126]. Conversely, exposure during adolescence to predictable chronic mild stress facilitates fear extinction and this appears to be related to increased BDNF/ERK1/2 signaling in infralimbic cortex in adulthood resulting from decreased DNA methylation of the *Bdnf* gene at exons IV and VI.

Clinical studies are also consistent with translational studies in showing that individuals with the low expression Val66Met single nucleotide polymorphism of *Bdnf* have impaired ability to extinguish learned fears [127], a diminished response to extinction-based therapies, and enhanced risk for developing fear-related disorders such as PTSD [128–130]. The Val66Met polymorphism is associated with reduced activity-dependent secretion of mature BDNF (mBDNF) [131,132] and it has been proposed that the corresponding decrease in mBDNF bioavailability results in reduced BDNF–TrkB-dependent signaling that affects the development of fear circuit plasticity during a sensitive period in early adolescence such that alterations in BDNF expression exert a persistent impact on fear behaviors and fear-related disorders [133].

However, that specific molecular mechanism has recently been challenged by the finding that the BDNF prodomain, which is cleaved off from BDNF along with mBDNF, is also secreted in an activity-dependent manner from neurons [134]. Further, it is structurally modified by the presence of the Met 66 amino acid and serves as a potent ligand that triggers disassembly of mature mushroom spines on ventral hippocampal CA1 neurons that project to prelimbic cortex and eliminates synapses by mobilizing actin regulators [134]. The net molecular effect of the BDNF Met prodomain is to keep the projections from ventral

hippocampal CA1 to prelimbic cortex in an immature developmental state thus attenuating their capacity for subsequent circuit modulation necessary for fear extinction [135]. Hence, the consistent cross-species effect of the BDNF Val66Met polymorphism on anxiety may not be due to reduced BDNF activity dependent release but to a specific pro-anxiety effect of the BDNF Met prodomain.

BDNF and Aggression

Most of what we know regarding the role of BDNF in aggression comes from preclinical studies. In one of the earliest reports, Lyons *et al.* (1999) [43] found that heterozygous BDNF(+/−) mice with reduced BDNF levels developed prominent intermale aggression, hyperphagia and weight gain, which were attributable to alterations in the expression of 5-HT receptor subtypes in the cortex, hippocampus, and hypothalamus and could be ameliorated by administration of selective serotonin reuptake inhibitors. Further studies showed that conditional knockout mice in which BDNF expression was disrupted either prenatally or postnatally became dramatically hyperactive and aggressive. BDNF depletion from the fetal brain had more pronounced effects on aggression and was associated with deficits in 5-HT(2A) receptor content in medial frontal cortex [136].

In general, *Bdnf* heterozygote knockouts or mice with forebrain-restricted full *Bdnf* deletions show elevated aggression, but also experience other changes such as increased anxiety [137]. Another important means of studying selective effects of *Bdnf* alterations is to produce mutant mice in which BDNF production from one of the major promoters (e.g., I, II, IV, or VI) is selectively disrupted. Mice with promoter I or II disruptions (*Bdnf* -e1 and -e2) displayed heightened aggression, increased sexual behavior, alterations in serotonin signaling [44] and hyperphagia [138]. In contrast, *Bdnf* -e4 and -e6 mutants were not aggressive or hyperphagic but displayed widespread impairments associated with GABAergic gene expression [44].

Clinical studies have reported a significant association between peripheral BDNF levels and aggression in a small sample of unmedicated participants with Obsessive-Compulsive Disorder and healthy controls [139] and in individuals with amnestic mild cognitive impairment or Alzheimer's disease [140]. The association between Val66Met polymorphism and aggression however is unclear. One study reported a significant association between number of BDNF 66Met alleles and overt aggression scores in patients with schizophrenia [141]. Another reported a significant G × E interaction in which childhood participants in the large Avon Longitudinal Study who affiliated with aggressive peers at age 10 showed increased risk for aggression at age 15 if they carried the BDNF Met-Met variant compared to Val-Val wildtype [142]. On the other hand, two studies failed to find a significant association between Val66Met polymorphisms and aggression in individuals with

schizophrenia [143,144]. This lack of consistency is not surprising given the complexity of human aggression, reliance on peripheral BDNF measures that can be problematic [145] and focus on the Val66Met polymorphism as we are unaware of any reports of increased aggression in mutant mice engineered to mimic this polymorphism.

BDNF, Orexin/Hypocretin and FOH

Overall, there is a wealth of data linking the beneficial psychiatric effects of ketamine to BDNF and altered BDNF levels within specific brain regions to the phenotypic features of FOH. We suspect however that the story does not end here, and a critical question remains as to why do alterations in BDNF levels within these regions produce this array of symptoms? Our leading hypothesis is that the orexin/hypocretin (orx/hcrt) system is also fundamentally involved and interacts with BDNF-TrkB to regulate these behaviors. Briefly, orx/hcrt neurons, colocalized with glutamate and other co-transmitters are expressed in a limited region of the hypothalamus comprised of the dorsal-medial hypothalamus (DMH), lateral hypothalamus (LH) and perifornical area (PFA) [146] but innervate a wide array of regions. Orexin 1 receptor mRNA is preferentially located in locus coeruleus, prefrontal and infralimbic cortex, hippocampus (CA2) and anterior hypothalamus. Orexin 2 receptor mRNA is located in the tuberomammillary nucleus, arcuate nucleus, dorsomedial and lateral hypothalamus, paraventricular nucleus, hippocampus (CA3) and medial septal nucleus [147]. Both receptor mRNAs can be found in the amygdala, bed nucleus of the stria terminalis, paraventricular thalamus, dorsal raphe, ventral tegmental area and laterodorsal tegmental nucleus (LDT)/pedunculopontine nucleus (PPT) [147,148]. The orx/hcrt system serves as a central mediator of reward/aversion [149–160], sleep/arousal [27,161–179], thermoregulation [180–184], energy homeostasis [185–196], motor control [197–200] response to stress or threat [201–213], and production of theta band oscillations that synchronize neuronal networks [27,214–216]. It is this circumscribed area of the hypothalamus, with only about 1000 cells, that coordinates diverse, contextually appropriate survival behaviors linked to homeostatic functions that cycle within the circadian day and oscillate in parallel with ultradian frequencies of arousal states during wake and sleep [32].

We particularly suspect that abnormalities within the orx/hcrt system may play a fundamental role in the emergence of FOH given its critical importance in thermoregulation [180–184] and sleep wakefulness [27,161–179]. Loss of orexin in knock out mice results in elevated nocturnal temperature due to inadequate activation of heat loss mechanisms or sustained activity in heat-generating systems and is associated with sleep fragmentation [182]. We propose that FOH, at its core, is a disorder involving the impaired homeostatic regulation of certain survival functions, the most dramatic being the dysregulation in threat perception and development of fear-based obsessions of harm

befalling the individual that may be initiated or induced by a disturbance in thermoregulation. We envision orx/hcrt as the output of a hypothalamic command center that orchestrates and coordinates between these various survival-based behaviors. In contrast, BDNF is locally expressed in the regions involved in generating these homeostatic processes and likely plays an important role in bringing these behaviors about once signaled by enhancing synaptic transmission, shifting the balance between excitatory and inhibitory neurotransmission and facilitating rapid plastic transformations. We suspect that FOH may represent a cluster of highly similar ketamine-responsive disorders involving a primary disturbance in either orx/hcrt or BDNF, though this remains to be determined.

DISCUSSION

In 1972, Feighner, Robins, Guze and Winokur [217] laid out a strategy for establishment of a psychiatric taxonomy. In their view psychiatric disorders could be distinguished by their symptoms, age of onset, clinical course, family history and laboratory measures. FOH readily emerges as its own unique disorder or subtype by this strategy. While FOH shares with bipolar disorder a severe and pervasive problem with mood dysregulation characterized by depression, irritability and at least brief periods of mania [9] it stands apart because of the thermoregulatory abnormality and the prodromal sequence of nightmares and REM intrusions leading to fear-based obsessions and an auto-traumatized state resembling PTSD. Further, a 'fear of harm' factor was found to be even more heritable than depression or mania factors [5] and the measurable disturbance in distal/proximal skin temperature at bedtime that results in delayed or absent DPG^0 could emerge, with further study, as a potential biomarker [3]. An important lesson is that the recognition of more homogeneous clusters within broad diagnostic categories may benefit from assessment of features, such as impaired thermoregulation, that go beyond our customary focus.

There is also increasing recognition that the Feighner *et al.* [217] approach, which has led us from DSM-III to DSM-5, is insufficient. As Insel *et al.* [12] articulated, symptom-based classifications must inevitably be flawed as two fundamentally different medical disorders can share the same syndromic manifestations and a common underlying cause may manifest in distinctly different ways. In the end a taxonomy for brain-based psychiatric disorders will require a specific understanding of the underlying molecular, cellular and circuit-based neurobiology. Hence, we have leveraged what we have learned regarding therapeutic effectiveness to hypothesize how ketamine may work to address the myriad symptoms of FOH and how they may arise from a disturbance in BDNF or the orx/hcrt system. Given the complexity of these systems it is also likely that FOH may have more dimensional properties than cross categorical boundaries [2].

We need to emphasize that while FOH is not listed in the DSM or ICD and relatively few clinicians may be aware of it, it is not a rare disorder. According to our data up to a third of youths who present with symptoms suggestive of bipolar disorder may have FOH [2]. Clinicians treating children, adolescents and emerging adults with severe highly comorbid treatment-refractory disorders will have likely encountered several without necessarily being aware of their unique features. Inquiring about heat sensitivity and cold tolerance, fear-based obsession, defensive aggression and nightmares may be revelatory. Though randomized controlled trials have not been conducted, clinical experience and blind chart review have found that these individuals typically have a good to excellent response to intranasal ketamine, which appears to work optimally when combined with lithium, and the benefits have endured for as long as the patients have been followed [4]. Hence, it is well-worth identifying these individuals as it may lead to a crucial change in therapeutic approach.

A number of important limitations need to be acknowledged. First, published information on FOH consist primarily of seven peer-reviewed articles [1–7] and there is need for independent replication. Hence, we strongly encourage colleagues who treat youths with severe mood disorders to screen for symptoms of FOH and report their results. Second, assessment of distal/proximal temperature gradients and actigraph-assessed sleep onset identified a potential biomarker, but this needs to be replicated and assessed for its capacity to distinguish FOH from other psychiatric disorders with disrupted sleep. Third, our hypotheses about the potential role of BDNF and orx/hcrt systems is based on clinical response to intranasal ketamine and literature review regarding the relationship between these neurotransmitter systems and the deep phenotypic features of FOH. We have not collected samples and do not have genetic, epigenetic or clinical chemistry findings to support these hypotheses.

In short, there is a tremendous amount of work that needs to be done. On the other hand, the patients that we have seen have been in dire straits—compelling us to apply what we have learned, rather than waiting for definitive pathophysiological answers. The identification of an underlying disturbance in thermoregulation and heat dissipation has been a critically important insight as it has led to complementary strategies such as use of cooling baths and bedside fans to improve sleep and overall well-being. We have also learned that individuals with FOH tend to become more symptomatic when exposed to abrupt changes in weather pattern so we can adjust accordingly and not mistake a transient weather-related disruption for a more fundamental change in their condition.

It is interesting that critical components of FOH are found in specific DSM disorders. Nightmare disorder captures the frequent, intensely disturbing dreams that wake the sleeper and the subsequent emergence of dysphoria without recognizing the risk for auto-traumatization and

symptoms of PTSD. DSM-5 now includes an "*anxious distress*" specifier for bipolar disorder or major depression which stems from the recognition that these individuals may have an increased risk for suicide and a particularly poor response to treatment. However, this specifier includes individuals with relatively mild symptoms of anxiety (feeling keyed up, unusually restless, difficulty concentrating) as well as individual who fear that something awful may happen or fear that they might lose control, which comes close to the concept of fear of harm that we propose is the overt manifestation of the underlying problem responsible for their poor prognosis. Overall, individuals with FOH typically receive an expanding list of DSM diagnoses throughout childhood. An advantage of the FOH construct, and focus on neurobiology, is the ultimate recognition that the diverse array of disparate appearing symptoms that constitutes their deep phenotype come together in a meaningful way and stem from a specific underlying cause rather than from an unfortunate combination of unrelated comorbidities. Ongoing studies should further clarify our understanding of this disorder.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization and organization of the paper and to the description of the phenotype. DP, SM and MHT conducted key literature reviews linking FOH to BDNF and orexin. DP and MHT primarily wrote the paper with critical input from all authors.

CONFLICTS OF INTEREST

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Research report

A strategy for identifying phenotypic subtypes: Concordance of symptom dimensions between sibling pairs who met screening criteria for a genetic linkage study of childhood-onset bipolar disorder using the Child Bipolar Questionnaire

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Abstract

Background: Specific symptom dimensions have been used to establish phenotypic subgroups in recent genetic studies of bipolar disorder. In preparation for a genetic linkage study of childhood-onset bipolar disorder (COBPD), we conducted an exploratory analysis of the concordance of prominent symptom dimensions between sibling pairs (N=260) who screened positive for COBPD. This report presents data on the potential usefulness of these dimensions in genotyping.
Method: A principal components factor analysis was conducted on the symptoms of 2795 children who screened positive for COBPD on the Child Bipolar Questionnaire (CBQ). The resulting factors were used in a concordance analysis between 260 proband/sibling pairs and 260 proband/matched comparison pairs.
Results: Ten factors were extracted. The strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between proband/sibling vs. proband/comparison pairs, were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep–wake cycle disturbances), and Factor 2 (Attention/Executive function deficits). Based on factor loadings and multivariate analyses, CBQ items were selected for a "Core Index" subscale that had a robust concordance estimate in the sibpair group (rho=0.514, 95% CI 0.450–0.577) as compared to the proband-matched comparison group (rho=0.093, 95% CI 0.008 to 0.178).
Limitations: Research diagnostic interviews (K-SADS P/L) were conducted to confirm bipolar diagnosis in only a subsample (N=100) of the children whose data were used for the concordance analysis.
Conclusions: Our data suggest a profile of heritable clinical dimensions in addition to classic mood symptomatology in COBPD. These features may represent a more homogeneous phenotypic subtype of COBPD that may prove more useful for delineating the neurobiology and genetics of the disorder than standard diagnostic models.

Keywords: Childhood-onset bipolar disorder; Pediatric bipolar disorder; Sib-pair concordance; Behavioural phenotype; Anxiety; Aggression; Child Bipolar Questionnaire

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1. Introduction

Over the past decade, several genetic loci have been mapped in bipolar disorder (BD), including 4p, 4q, 8q, 10p, 12q, 13q, 18q, 21q and 22q (reviewed by MacQueen et al., 2005; Payne et al., 2005). However, with the exception of the disruption of the DISC1 gene, which occurs as a consequence of a rare 1:11 (q42.1; q14.3) translocation identified in a Scottish family with schizophrenia and BD (St Clair et al., 1990), no functional alleles have been unequivocally identified. In addition, independent replication at positive loci is not universal, probably because of genetic heterogeneity and a lack of homogeneous phenotypes (Faraone and Tsuang, 2003; Tsuang et al., 2004; Lin et al., 2005; MacQueen et al., 2005).

It has been suggested that age of onset could be used to separate patients into more homogeneous phenotypic subgroups for genetic studies (reviewed by Leboyer et al., 2005). One subgroup of BD that holds promise for establishing a distinct, more uniform phenotype for genetic analysis is childhood-onset bipolar disorder (COBPD). Probands with COBPD have been found to have family pedigrees with higher rates of bipolar disorder in first degree relatives, including siblings with similar age of onset (Todd et al., 1993; Leboyer et al., 1998; Bellivier et al., 2003; Chang et al., 2003; Papolos, 2003; Faroane et al., 2004a; Leboyer et al., 2005). The study of COBPD may be particularly useful in identifying structural, biochemical and functional endophenotypic markers of the illness in the brain (Frazier et al., 2005).

It has also been suggested that dimensional criteria may prove more useful than categorical definitions in etiological research (Kendell and Jablensky, 2003). While categorical definitions tend to obscure symptoms not central to the construct of a particular disorder, i.e. the DSM-IV caveat "Do not include if better accounted for by another disorder," the individual symptoms or constellations of symptoms associated with a condition may yield important clues to its biological underpinnings. In their recent, extensive review of the findings of clinical, epidemiological, neurobiological, and genetic studies in bipolar disorder, Hasler et al. (2006) concluded that particular symptom dimensions, deficits, and physiological and neuroanatomical anomalies deserve further research focus as candidate endophenotypes that could improve the phenotypic definition of bipolar disorder.

In genomics, the importance of the analysis of symptom dimensions as a strategy for genotyping is becoming more evident. In a recent genetic study of bipolar disorder pedigrees ascertained through adult probands, Faraone and colleagues (2004b) quantified dimensions of bipolar symptoms derived from a principal components factor analysis, determined their heritability, and used the heritable factors in a variance-components linkage analysis. More recently, Cheng et al. (2006) used both standard diagnostic models and comorbid symptoms of psychosis, suicidal behavior and panic disorder to identify phenotypic subtypes for a genome-wide linkage scan in a large bipolar sample. Over half the regions implicated by the strongest linkage signals (genome-wide significance) were identified using phenotypic subtypes. Cheng and colleagues suggest that, "dissection of the disease phenotype can enrich the harvest of linkage signals and expedite the search for susceptibility genes."

In previous work with data collected from the parents of a large sample of clinically diagnosed bipolar children ($N=1601$) via the Juvenile Bipolar Research Foundation (JBRF), we observed a strong relationship between frequent and intense fears about harm coming to self and others and overt aggressive acts toward self and others (Papolos et al., 2005). These data indicated that bipolar children/adolescents identified as having high fear-of-harm anxieties were 2.7-fold (RR=2.68) more likely to be identified by their parents as engaging in severely self-injurious behaviors than subjects with relatively low fear-of-harm anxieties; and these same children were 8-fold (RR=7.97) more likely to be identified as engaging in severely injurious assaults on others. There was a sharp difference in average fear-of-harm index between subjects with a clinical bipolar diagnosis ($N=1601$) and a sample of children in the JBRF database who did not have a clinical diagnosis of bipolar disorder ($N=661$) ($p<0.0001$).

Fear-of-harm, as a symptom dimension, appears to represent significant symptoms of anxiety and obsessiveness. Anxiety in COBPD has been the subject of several recent studies (Dilsaver and Chen, 2003; Masi et al., 2004; Post et al., 2004, Dickstein et al., 2005; Harpold et al., 2005). Consistent with Fear-of-harm as a primary symptom dimension in COBPD are findings from a recent study by Rich et al. (2006) that examined neural mechanisms mediating face processing in bipolar youth. These investigators found that in comparison to normal controls, patients perceived greater hostility in neutral faces and reported more fear when viewing them. Additionally, patients had greater activation in the left amygdala when rating face hostility, and their fear of the face, when compared to controls. Interestingly, neuroimaging findings in obsessive-compulsive disorder (OCD) and other anxiety disorders, such as social phobia, suggest parallels to the neuroimaging data in bipolar disorder (Stein et al., 2002; Mataix-Cols et al., 2003, 2004; Phillips and Mataix-Cols, 2004; Williams et

al., 2006). The comorbidity of panic and bipolar disorders has suggested to some a possible genetic subtype of bipolar illness (MacKinnon et al., 2002, 2003a,b; Rotondo et al., 2002; Cheng et al., 2006).

In order to gather preliminary data to test the hypothesis that the fear-of-harm symptom dimension may be a clinical marker germane to bipolar disorder heritability, especially COBPD heritability, we conducted an exploratory analysis of the concordance of it and other symptom dimensions between several hundred sibpairs enrolled in a JBRF-sponsored genetics study with a longitudinal component. Our findings suggest that a dimensional approach to COBPD will be an appropriate diagnostic strategy to pursue for future genetic studies.

2. Methods

2.1. Data acquisition

The JBRF has established an extensive Internet-based system for data acquisition on children clinically diagnosed with bipolar disorder. Parents and primary caregivers through national advocacy sites, online newsletters, and their children's clinicians have entered clinical and demographic data on their children to a secure domain on the JBRF website. Parent report indicates that approximately 69% of these children have been diagnosed with bipolar disorder by a psychiatrist, psychologist, neurologist, or pediatrician in the community.

Families with more than one affected child are identified by the JBRF data acquisition program and are informed of their initial eligibility for a JBRF-sponsored genetic linkage study. Through this method, 445 affected sibling pairs were identified, including a proband and at least one full biological sibling who screened positive for bipolar disorder using the Child Bipolar Questionnaire.

2.2. Initial screening and diagnostic confirmation

The Child Bipolar Questionnaire (CBQ) is a parent-report form that was developed to assist in the rapid identification of homogeneous subgroups of children with BD (Papolos et al., 2006). The majority of the CBQ's 65 items are drawn from DSM-IV symptom criteria for mania and major depression, but symptoms of common comorbid conditions, such as anxiety and behavior disorders, are also represented. Items are rated on a Likert scale: "1—never", "2—sometimes", "3—often", or "4—very often or almost constantly". In preliminary inquiries, the CBQ has demonstrated excellent reliability and validity in identifying subjects that meet a K-SADS diagnosis of bipolar disorder (inclusive of BPI, BPII, and BP-NOS) (Papolos et al., 2006).

The CBQ total score is the count of items rated "3" or "4". Sibling pairs were considered initially eligible for participation in the genetic linkage study if they both scored ≥ 40 out of 65 items on the CBQ. Diagnostic confirmation of these sibling pairs by administration of the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Version (K-SADS P/L) (Kaufman et al., 1997) is underway.

2.3. Factor analysis

In order to identify a set of prominent symptom dimensions that could be used to create homogeneous subgroups for genotyping, a series of principal component factor analyses with Varimax rotation were carried out on CBQ symptom data from the larger JBRF database of children with a CBQ total score ≥ 40 ($N=2795$).

2.4. Concordance analysis of factors

Concordance estimates between eligible sibpairs were then calculated for the factors resulting from the factor analysis. Multiple sibships were handled by selecting the sibling of the same sex as the proband and closest in age as the identified sibling for the concordance analysis. Inclusion criteria limited the siblings to be within 4 years of age of each other. If there was no affected sibling of the same sex as the proband, then the affected sibling of the opposite sex and closest in age was selected. For each identified affected sibpair, a comparison subject of the same age (in years) and sex as the proband was selected from the families in the database with only one child who screened positive for BD. This procedure resulted in the selection of sets of 3 subjects (probands, siblings, and non-related comparison subjects) that formed the study sample for this investigation.

Concordance estimates between responses of probands and siblings were obtained using the method of Lin (1989). This procedure yields a concordance coefficient ("rho") and an estimate of its 95% confidence interval (95% CI). Concordance coefficients were estimated for both proband/sibling pairs and proband/comparison pairs. Because the proband/comparison concordance was dependent on the random (within age/sex category) selection of a comparison subject for each proband, we repeated the selection procedure multiple (1000) times, using bootstrap methods to obtain the estimated proband/comparison concordance

coefficient and its standard error. These rho-estimates were then differenced to provide an estimate of the proband/sibling vs. proband/comparison concordances. An estimate of the standard error of this rho-difference estimate was obtained, and a *z*-statistic calculated as the ratio of the rho-difference to its standard error was obtained. The associated *p*-value was obtained from standard normal tables.

2.5. Concordance analysis of Y-BOCS derived fear-of-harm index

In our previous examination of the fear-of-harm symptom dimension (Papolos et al., 2005), we used a Y-BOCS measure that consisted of a count of six aggressive obsessions rated by the parent as occurring at a frequency of "3" ("often") or "4" ("very often or almost constantly"): [1] Fear might harm self; [2] Fear might harm others; [3] Fear harm might come to self; [4] Fear harm will come to others (may be because of something child did or did not do); [5] Fear will act on unwanted impulses (e.g., to stab a family member); [6] Fear will be responsible for something else terrible happening (e.g., fire, burglary, flood). Where Y-BOCS data were available, this Y-BOCS-derived fear-of-harm index was included in the current concordance analysis between eligible sibpairs.

2.6. Concordance analysis of CBQ subscale of items found to correlate with fear-of-harm

In an effort to better characterize a phenotypic subgroup that had the fear-of-harm symptom dimension, a correlation analysis of CBQ items with the YBOCS fear-of-harm index was conducted to identify associated symptoms that could assist in genotyping. This analysis was limited to CBQ items not directly represented in the YBOCS data. The resulting items were used to comprise a scorable subscale of the CBQ, dubbed the Core index that was analyzed for concordance between proband/sibling and proband/comparison pairs.

2.7. General statistical methods

Averaged continuous data are reported as means with standard deviations (mean ± SD) or 95% CI. Binary data are reported as *N* (%) or *N*/denominator (% with 95% CI). Some continuous variables were logarithmically transformed to achieve more nearly Gaussian distributions. Robust standard error (SE) estimates were obtained whenever feasible. Statistical significance required 2-tailed $p \leq 0.05$. Analyses employed commercial microcomputer programs (Stata®, Stata Corporation, College Station, TX).

3. Results

3.1. Age and sex data

Twenty-three hundred forty-six parents provided CBQ data for 2795 children/adolescents via the JBRF internet-based system. Of these, 70% (1957) were singletons, 688 were full biological sibling pairs; and the remaining 150 children were members of multiple affected sibships. As noted in Methods, inclusion criteria limited the siblings to be within 4 years of age of each other and sibpair selection was prioritized by sex. That is, for male probands, the selection algorithm gave preference to male matching siblings, provided that the 4-year age criterion was satisfied; and similarly, for female probands, priority was assigned to female siblings. Using these methods, 260 sibpair (proband/sibling) groups were selected. Comparison subjects were randomly selected within age/sex strata from the subset of the available set of subjects that scored >40 on the CBQ for whom the parents did not provide data on a sibling ($N = 1957$). The random selection resulted in 260 comparison subjects matched by age (same age by year) and sex to the probands selected for inclusion in the study sample Age/sex and previous diagnosis data for the probands/siblings/comparisons are summarized in Table 1. It is noticeable that the selection algorithm yielded a set of study triples (probands/siblings/comparisons) for whom the within-sibling age differences and sex ratios were quite minor.

3.2. Results of factor analysis of CBQ item-level data

Ten factors with eigenvalues >1.0 were identified based on CBQ data for the entire sample of 2795 subjects. These ten factors are listed in Table 2 along with their corresponding CBQ items. The factors are named based on item content. Among the symptom dimensions represented by the factors are a combination of anxiety symptoms and overt aggressive behaviors (Factor 9) that parallels our previous findings with the Y-BOCS fear-of-harm data. In addition, there is a factor representing aggressive behavior without the anxiety component (Factor 5) and one representing anxiety symptoms without the aggressive component (Factor 10).

3.3. Results of concordance analysis of 11 factors

Concordance coefficients (Lin, 1989) for these CBQ factors were estimated between probands and siblings

Table 1
Study sample characteristics

	Proband	Sibling	Control	χ^2 [df=2]	p
Participants (N)	260	260	260	–[a]	–
Sex: All subjects (N/% male)	170 (65.4%)	149 (57.3%)	160 (65.4%)	–[b]	–
Sex of sibling:					
Male probands[c]	–	96/170 (56.5%)	170/170 (100%)	–[b]	–
Female probands[c]	–	52/90 (57.8%)	90/90 (100%)	–[b]	–
Age	11.1±3.6	11.0±3.6	11.1±3.6	–[b]	–
Diagnosis:					
Bipolar disorder	179 (68.9%)	171 (65.8%)	180 (69.2%)	0.99	0.61
Comorbid diagnoses:					
Attention deficit disorder	151 (58.1)%	150 (57.7%)	154 (59.2%)	0.15	0.93
Obsessive-compulsive	55 (21.2)%	60 (23.1%)	50 (19.2%)	1.16	0.56
Generalized anxiety disorder	54 (20.8%)	45 (17.3%)	50 (19.2%)	1.43	0.49

a. χ^2-statistic obtained by generalized linear regression modeling methods, with adjustment for clustering within matched group of proband/sibling/control.
b. χ^2-statistic not calculated for sex and age differences within proband/sibling/control matched groups because sex and age were two of the selection criteria used to select the matched groups.
c. Number (%) of males within families with either male or female probands.

Table 2
CBQ principal component factors

Factor[a]	Eigen-value	Mean± SD[b]	CBQ item content
I. Oppositional/Poor frustration tolerance	14.0	8.1±2.5	Is intolerant of delays; Relentlessly pursues needs/demanding of others; Is willful, refuses to subordinate to others; Argues with adults; Is bossy towards others; Defies or refuses to comply with rules; Blames others for his/her mistakes; Is easily angered in response to limit setting; Has protracted, explosive temper tantrums*
II. Attention/Executive functions deficit	3.9	7.8±2.4	Is easily distracted by extraneous stimuli; Is easily distracted during repetitive chores; Demonstrates inability to concentrate at school; Attempts to avoid homework assignments; Able to focus well but also easily distractible; Has poor handwriting; Has difficulty organizing tasks; Has difficulty making transitions; Has difficulty estimating time; Has auditory processing/short-term memory deficit
III. Depression	3.6	5.4±2.0	Complains of being bored; Has periods of low energy or withdrawal; * Has decreased initiative; * Has periods of self doubt/poor self-esteem; * Feels easily criticized and/or rejected; Feels easily humiliated or shamed; * Has made clear threats of suicide
IV. Sensory sensitivity	3.0	2.3±1.5	Is extremely sensitive to textures of clothes; Exhibits extreme sensitivity to sound ; Complains of body temperature extremes; * Has concern with dirt, germs, contamination*
V. Aggression	2.5	4.9±2.7	Has difficulty maintaining friendships; Displays aggressive behavior towards Others; * Has destroyed property intentionally; Makes moderate threats to others or self; Makes clear threats of violence to others/self; Has made clear threats of suicide; Fascinated with gore, blood, violent imagery
VI. Sleep cycle problems	2.1	4.0±1.7	Has difficulty arising in the AM; Is hyperactive and easily excited in the PM; Has difficulty settling at night; Has difficulty getting to sleep; * Sleeps fitfully and/or awakens in the night; Has night terrors and/or nightmares*
VII. Grandiose/Hypersex	1.6	2.6±1.5	Has exaggerated ideas about self or abilities; Tells tall tales/embellishes or exaggerates; Displays precocious sexual curiosity; Exhibits inappropriate sexual behaviors; Lies to avoid consequences of actions*
VIII. Mania	1.3	6.5±1.9	Is hyperactive and easily excited in the PM; Is easily excitable has periods of high energy, frenetic activity; Has many ideas at once; * Interrupts or intrudes on others; * Has periods of excessive and rapid speech; Displays abrupt, rapid mood swings; * Has elated or silly/giddy mood states*
VIIII. Fear of harm	1.3	5.2±2.8	Displays excessive distress when separated; * Exhibits excessive anxiety or worry; * Has night terrors and/or nightmares; * Displays aggressive behavior towards others; * Has destroyed property intentionally; Makes moderate threats to others or self; Makes clear threats of violence to others/self
X. Anxiety	1.1	1.5±1.0	Displays excessive distress when separated from family; Exhibits excessive anxiety and worry; Has night terrors and/or nightmares

* Item chosen for Core Index subscale.
[a] Factors identified limited to factors with eigenvalues ≥1.0.
[b] Factor summary scores (mean±SD) are based on the several CBQ items most closely correlated with each factor.

and, separately, between probands and matched comparison subjects. These data are summarized in Table 3.

The strongest concordance coefficients (rho) between probands and siblings and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep–wake cycle disturbances), and Factor 2 (Attention deficits). For example, for Factor 9 (Fear of harm), the proband/sibling rho estimate (0.287) was substantially larger than the corresponding proband/comparison rho estimate (0.018), and this difference was statistically significant ($z=3.19$, $p<0.001$; Table 3). Similarly, for Factor 5 (Aggression), the two estimates for rho were 0.246 vs. 0.014, and this difference was statistically significant ($z=2.74$, $p=0.006$; Table 3). It is noteworthy that all of the rho coefficients for the proband vs. comparison pairs were near zero (as expected because of the random selection of comparisons).

For several of the CBQ factors, the proband vs. sibling concordances were found to be relatively weak. For the factor assessing classic adult manic symptoms (Factor 8), the rho coefficient was smaller than 0.10, although the majority of the larger group ($N=2795$) were reported to often or almost always experience the eight symptoms included in this factor (Displays abrupt, rapid mood swings [88.8%], Interrupts or intrudes on others [87.4%], Has periods of high frenetic energy [84.4%], Is easily excitable [86.2%], Has elated or silly/giddy mood states [80.6%], Is hyperactive in the PM [78.8%], Has many ideas at once [76.4%], Has periods of excessive and rapid speech [73.3%]), and the mean number of these symptoms reported was 6.52. Possible reasons for this finding are examined in Discussion.

3.4. Results of concordance analysis of Y-BOCS-derived fear-of-harm index

Y-BOCS data were available on 249 sibling pairs. The concordance estimate for the Y-BOCS-derived fear-of-harm index was also substantially and significantly different from zero (rho=0.341, 95% CI 0.231–0.451, $p<0.001$).

3.5. Results of correlation analysis of CBQ items with fear-of-harm

We hypothesized that 17 CBQ items would be strongly associated with fear of harm in the children that screened positive for bipolar disorder: 2) exhibits excessive anxiety or worry; 8) has night terrors and/or nightmares; 41) feels easily criticized and/or rejected; 42) feels easily humiliated or shamed; 45) relentlessly pursues own needs and is demanding of others; 46) is willful and refuses to be subordinated by others; 50) blames others for his/her mistakes; 51) is easily angered in response to limit setting; 53) has protracted, explosive temper tantrums; 55) displays aggressive behavior towards others; 56) has destroyed property intentionally; 57) curses viciously, uses foul language in anger; 58) makes moderate threats to others or self; 59) makes clear threats of violence to others or self; 61) is fascinated with gore, blood, or violent imagery; 62) has acknowledged experiencing auditory and/or visual hallucinations; 64) has concern with dirt, germs, or contamination. In bivariate analyses, all 17 of these

Table 3
CBQ factor concordance contrasted between sibpairs (proband vs. sibling) and non-sibpairs (proband vs. comparison)

Factor		Proband vs. Sibling	Proband vs. Control	z [a]	p
		rho [b] (95% CI)	rho [b] (95% CI)		
Factor 9	Fear of harm	0.287 (0.18, 0.40)	0.018 (−0.10, 0.14)	3.19	<0.001
Factor 5	Aggression	0.246 (0.13, 0.36)	0.014 (−0.11, 0.14)	2.74	0.006
Factor 10	Anxiety	0.177 (0.06, 0.29)	−0.029 (−0.15, 0.09)	2.38	0.017
Factor 4	Sensory sensitivity	0.182 (0.06, 0.30)	−0.016 (−0.14, 0.10)	2.30	0.022
Factor 6	Sleep/wake disturb	0.236 (0.12, 0.35)	0.043 (−0.08, 0.16)	2.27	0.023
Factor 2	Attention/Executive deficit	0.153 (0.03, 0.27)	−0.036 (−0.15, 0.08)	2.21	0.027
Factor 3	Depression	0.251 (0.14, 0.36)	0.079 (−0.04, 0.20)	2.04	0.041
Factor 7	Grandiose/Hypersexual	0.114 (−0.01, 0.23)	−0.017 (−0.14, 0.10)	1.51	0.13
Factor 8	Mania	0.092 (−0.03, 0.21)	0.019 (−0.10, 0.14)	0.83	0.40
Factor 1	Oppositional/Poor frustration	0.042 (−0.08, 0.16)	0.081 (−0.03, 0.19)	0.46	0.65
CBQ Total Score		0.314 (0.20, 0.42)	0.016 (−0.10, 0.14)	3.59	<0.001

[a] z-statistic obtained by generalized linear regression modeling methods, with adjustment for clustering within matched proband/sibling/control set.
[b] rho is concordance coefficient (Lin, 1989), together with its 95% confidence interval (95% CI).

CBQ items were found to be strongly correlated with the Y-BOCS-derived fear-of-harm score. All 17 of these bivariate associations, examined with Poisson modeling methods (because the fear-of-harm score is a count with Poisson-like properties), were found to be strongly statistically significant. When these 17 items were examined in a series of multivariate analyses that included age and sex to estimate their correlations with the Y-BOCS fear-of-harm indicator, 12 items were found to have the most predictive value.

3.6. Results of concordance of CBQ Core Index subscale

In addition to the 12 items that remained after multivariate analyses, 10 CBQ items were identified based on the strength of their individual correlations with the Y-BOCS-derived fear-of-harm measure, their factor loadings, and the relevance of their content. Through this method, a single scorable subscale was created that could be used to rapidly identify a phenotypic subtype. The items included in this subscale, called the "Core Index," are listed in Table 4. The Core Index was found in preliminary investigations to have excellent validity (Papolos et al., 2006). The concordance estimate for the CBQ Core Index score (number of items rated "3—often" or "4—almost always") was found to be quite robust in the sibpair group (rho = 0.514, 95% CI 0.450–0.577). In contrast, the corresponding concordance coefficient for proband vs. matched comparison on this measure was near zero (rho = 0.093, 95% CI 0.008–0.178).

Table 4
CBQ core index subscale

1) displays excessive distress when separated from family
2) exhibits excessive anxiety or worry
6) has difficulty getting to sleep
8) has night terrors and/or nightmares
10) craves sweet-tasting foods
23) complains of body temperature extremes or feeling hot despite neutral ambient temperature
26) has many ideas at once
27) interrupts or intrudes on others
31) displays abrupt, rapid mood swings
32) has irritable mood states
33) has elated or silly, goofy, giddy mood states
36) takes excessive risks
38) has periods of low energy and/or withdraws or isolates self
39) has decreased initiative
40) experiences periods of self doubt and poor self-esteem
42) feels easily humiliated or shamed
52) lies to avoid consequences of his/her actions
53) has protracted, explosive temper tantrums
55) displays aggressive behavior towards others
62) has acknowledged experiencing auditory and/or visual hallucinations
63) hoards or avidly seeks to collect objects or food
64) has concern with dirt, germs, or contamination

4. Discussion

The methodology reported here is in keeping with the direction that a number of researchers who study the genetics of psychiatric illness have taken to further refine phenotypes for genotyping. Advances in genomics, cognitive neuropsychology, and brain imaging techniques offer new possibilities for the *in vivo* study of the pathophysiology of neuropsychiatric disorders, including bipolar disorder. Researchers may now combine endophenotypic markers with refined clinical correlates to establish more distinct behavioral phenotypes. The identification of symptom dimensions such as fear-of-harm, strongly concordant in sibpairs who screened positive for COBPD, may suggest endophenotypes that could prove useful in clinical and etiological research.

In this group of preliminary analyses performed in preparation for a genetic linkage study of COBPD, 10 factors were extracted from a very large set of symptom level data reported by parents of children who met initial screening criteria for bipolar disorder. These factors were then analyzed for concordance between probands and siblings. The strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs, were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep–wake cycle disturbances), and Factor 2 (Attention/Executive function deficits). None of the factors with the strongest concordance contribute to current categorical definitions of bipolar disorder. The concordance estimate for Factor 8 (Mania), which includes CBQ items representing classic adult manic symptomatology, was relatively low. Yet of the eight items included in the mania factor, the mean number rated "3—often" or "4—almost always" was 6.52 in the larger sample from with the sibpair subjects were drawn.

The explanation for this intriguing finding may involve both age- of-onset and developmental changes in symptom presentation. Systematic clinical investigations and family/genetic studies have provided increasing evidence that the clinical presentation and naturalistic course of COBPD is substantially different from the adult-onset form of the disorder (Faedda et al., 1995, 2004; Wozniak et al., 1995; McElroy et al., 1997;

Wozniak and Biederman, 1997; Papolos and Papolos, 1999; Geller et al., 2002, 2004). This may be, in large part, due to developmental factors (Geller et al., 1998). In this investigation, we required that siblings be within 4 years of each other in age. However, this 4 year age difference may represent pre-vs. post-pubertal onset or other significant developmental differences that may affect symptom presentation. The comparison of symptom concordances between subgroups of sibling pairs in which age of onset and differences in developmental phase are focuses of study is an important direction for future research.

The CBQ-derived Factor 9 (Fear of harm), composed of symptoms of anxiety and aggressive behavior, was found to have a strong concordance (rho = 0.287) between probands and siblings who screened positive for bipolar disorder. This finding was not instrument-specific. The Y-BOCS derived fear-of-harm index, similarly composed of obsessive fears and strongly related to overt aggression, also had a substantial and statistically significant concordance between probands and siblings (rho = 0.341). This finding may parallel earlier descriptions of a phenotype of bipolar disorder in adolescents associated with comorbid separation anxiety and obsessive compulsive symptoms (Lewinsohn et al., 2000). The fear-of-harm symptom dimension may be a heritable feature of COBPD that characterizes a phenotypic subgroup who are described as fearful, irritable and explosive in clinical samples. In our current nosology, these potentially important phenotypic dimensions are frequently subsumed under the categories of commonly diagnosed comorbid anxiety and behavior disorders.

In the clinical realm of adult bipolar disorder, symptoms of paranoia, poor frustration tolerance, aggressive behavior, and severe anxiety, though not specifically included in the DSM-IV categorical definition of mania, are recognized associated features of the illness. These features clearly correspond well with a number of the factors that emerged in the dimensional analysis of this large set of symptom data from children who screened positive for BD. Included as an aggregate measure with symptoms of mania, depression, anxiety and aggression, additional symptoms that may be particularly salient in COBPD – sleep disturbance, disturbance in temperature regulation, circadian rhythm instability, and carbohydrate craving – had a high potential heritability in sibling pairs who screened positive for BD. We suggest that these are important dimensions of COBPD worthy of further study, as they may be representative of a core phenotype defined by terminology that more closely fits our current understanding of CNS systems and their behavioral correlates.

4.1. Limitations and caveats

Research diagnostic interviews (K-SADS P/L) were conducted to confirm bipolar diagnosis in only a subsample (N=100) of the children whose data was used for the concordance analysis. For pragmatic reasons, it was impossible to conduct diagnostic interviews with the entire sample (N=2795) who screened positive for BD on the CBQ. Therefore, the majority of the CBQ data used in the principal components analysis and in the concordance estimates is contingent upon accuracy of parent report. The CBQ has been validated against the K-SADS P/L (k=0.84), and recent research demonstrates a positive association between parent-rated mania symptoms and consensus BD diagnosis in adolescents (Hunt et al., 2005).

4.2. Conclusions

Traditionally, diagnostic definitions of bipolar disorder embedded in our psychiatric nomenclature have embodied the Kraepelinian concepts of mania and depression. Contemporary categorical distinctions between BD subtypes have been primarily concerned with episode duration and the presence or absence of classic manic symptoms. Standard diagnostic interviews are designed to make categorical decisions based on these definitions while either subsuming symptom dimensions not considered central to the construct of bipolar disorder or diagnosing them as central to a comorbid disorder. Thus, our assessment tools continue to support the current categorical definitions, perhaps masking information that might be crucial to understanding the etiology of the disorder. The use of rating scales covering multiple symptom dimensions allows symptoms that might be viewed as frequently co-occurring, but not central to a disorder, to become a focus of study. Our data suggest a heritable profile of clinical dimensions in COBPD that parallels commonly observed features of adult-onset bipolar disorder. Although not included in the categorical definition of mania, these symptom dimensions are consistent with evidence from diverse fields of inquiry implicating anomalies in a neural circuit involving the amygdala and the anterior cingulate cortex in the neurobiology of bipolar disorder (Davidson, 2000; Hariri et al., 2000, 2003; Allman et al., 2001; Phan et al., 2002; Strakowski et al., 2004; Haller et al., 2005; Blumberg et al., 2005; Chen et al., 2006; Rich et al., 2006). As phenotypic features, they may,

therefore, assist in identifying a homogeneous subtype of COBPD that could provide a more optimal venue for delineating the genetics of the disorder.

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Research paper

Clinical experience using intranasal ketamine in the longitudinal treatment of juvenile bipolar disorder with fear of harm phenotype

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ABSTRACT

Objectives: Fear of Harm (FOH) is a pediatric onset phenotype of bipolar disorder (BD) characterized by BD plus treatment resistance, separation anxiety, aggressive obsessions, parasomnias, and thermal dysregulation. Intranasal ketamine (InK) in 12 youths with BD-FOH produced marked improvement during a two-week trial. Here we report on the open effectiveness and safety of InK in maintenance treatment of BD-FOH from the private practice of one author.

Methods: As part of a chart review, patients 18 years or older and parents of younger children responded to a clinical effectiveness and safety survey. Effectiveness was assessed from analysis of responses to 49 questions on symptomatology plus qualitative content analyses of written reports and chart review. Adverse events (AEs) were analyzed by frequency, duration and severity. Peak InK doses ranged from 20 to 360 mg per administration.

Results: Surveys were completed on 45 patients treated with InK for 3 months to 6.5 years. Almost all patients were "much" to "very much" improved clinically and in ratings of social function and academic performance. Significant reductions were reported in all symptom categories. There were 13 reports of persistent AEs, none of which resulted in discontinuation. Acute emergence reactions were sporadically observed in up to 75%, but were mild and of brief duration.

Limitations: Retrospective review from a single practice without placebo control with potential for response and recall bias.

Conclusions: InK every 3–4 days at sub-anesthetic doses appeared to be a beneficial and well-tolerated treatment. Use of InK may be considered as a tertiary alternative in treatment refractory cases. Randomized control trials are warranted.

1. Introduction

The FOH phenotype of BD (BD-FOH) is a clinically distinct behavioral phenotype with early age of onset, severe manic and depressive symptoms, early and frequent psychiatric hospitalizations, significant social impairment and school problems (Papolos et al., 2009). Characteristics of this phenotype, and its high rate of heritability, were established in a sample of youths with clinician-assigned diagnoses of BD (N = 1601) (Papolos et al., 2005) and further verified in a large (N = 5335) community sample of children with bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BD (Papolos et al., 2009).

Clinically, it appears that a specific developmental sequence of fear-based (or sensitized) behaviors arises in these individuals and includes night sweats, recurrent night-terrors and vivid nightmares, obsessive bedtime rituals, fear of the dark, separation anxiety, hypervigilance, misperception of neutral stimuli as threatening, reactive aggression in response to limit setting or perceived threat or loss (Papolos et al., 2009). Individuals with FOH also tend to be remarkably cold tolerant and heat intolerant. We have proposed that this phenomenon may be a

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putative biological marker, indicative of a thermoregulatory disturbance in a thermosensory pathway that mediates heat-defense responses (Murphy et al., 2014).

The ability of ketamine to decrease fear sensitization and (dose-dependently) reduce body temperature in animals (Fahim et al., 1973; Pietersen et al., 2006) was the rationale for off-label use of intranasal ketamine (InK) in BD-FOH children. An open-label trial (Papolos et al., 2013) found a substantial, rapid reduction in measures of mania, fear of harm and aggression and significant improvement in mood, anxiety, attention/executive functions in 12 treatment-refractory youth, 10 males 2 females aged 6–19 years. InK every third day during a two-month period also led to remission of symptoms associated with the core features of the FOH phenotype and normalization in thermoregulation. Two questions remained unanswered; could this response be sustained, and was InK tolerable and safe with regular exposure over an extended period of months to years? Herein, we report results from the maintenance use of InK in 45 cases with BD-FOH, mean age 15.6 ± 6.7 years in one clinical practice. To our knowledge, this is the first report to describe sustained effectiveness, tolerability and safety of InK in the treatment of treatment-resistant mood-disorder patients over an extended period.

2. Methods

2.1. Participants

60 patients who met DSM-IV criteria for bipolar disorder as well as the FOH phenotype and demonstrated treatment resistance to traditional mood-stabilizing agents and atypical neuroleptics, were ascertained through the private practice of one of the authors (DFP). Written consent of patients was obtained after informed consent was provided about the risks of short-term and long-term ketamine. As part of a thorough clinical appraisal, information on side-effects and effectiveness was obtained from patients (if aged 18 or older) or parents through regular clinical contact and a retrospective survey. All patients were treated with InK and closely followed for 3 months to 6.5 years.

2.2. Administration and dosing

Patients were administered InK, as 0.1 ml sprays of 50–200 mg/ml ketamine in 0.01% benzalkonium chloride to alternating nostrils. Patients were instructed to administer sprays until a minimum intolerable dose (MID) was found and to repeat this administration every 3–4 days. If a satisfactory clinical response was not sustained for at least 3 days (as determined by twice weekly clinical evaluation), doses were raised incrementally by increasing the number of intranasal sprays until a new MID was achieved, or there was an 80% or greater reduction in symptom severity.

2.3. Chart review

A retrospective chart review was conducted by two independent raters (MHT, LCHG). Raters reviewed clinician notes, redacted to remove identifying information. The Clinical Global Impression Severity scale (CGIs) (National Institute of Mental Health, 1985) was used to rate the patient's overall clinical status prior to initiation of treatment as well as their most recent status on ketamine. The CGI – Improvement (CGIi) scale was used to record their overall degree of improvement based on all treatment notes.

2.4. Survey

All patients treated for ≥ 3 months and parents (if patient < 18 years of age) were invited to complete a survey of their retrospective observations of treatment response and side-effects. Measures were obtained through Likert scale responses that provided a measure of severity of symptoms both before and after ketamine for each category. The survey contained 49 items rated according to indices of severity or frequency and converted to 1–4 numerical scores.

Patients/parents were also asked to provide a narrative of the long-term use of ketamine, which was subjected to qualitative content analysis (Mayring, 2000). Briefly, this is a multistep process, guided by the key research question as to what were the primary positive and negative spontaneously reported features or outcomes of InK ketamine. The narratives were read and re-read many times to formulate tentative categories, which were discussed and within a feedback loop were revised and eventually reduced to main categories and checked regarding their reliability. We then determined, for each category, the percent of narratives in which the category was reported and the percentage of those reports that were endorsed in a positive manner. For two broad categories (overall degree of improvement and degree of improvement in work or school performance) results were coded using CGI-improvement scale.

For some analyses, patients were divided into two groups; those who had discontinued ketamine use (non-continuers), and those who continued to use ketamine at the time the questionnaire was completed (continuers). The questions for non-continuers comprised three sections: 1) reasons for discontinuation, 2) health issues and 3) side effects experienced during treatment. Questions for continuers included questions on age, weight, current dose, treatment summary, acute and enduring side-effects, health issues, life measures, and questions on behaviors and symptoms pre and post treatment. Each question was answered using a Likert scale that ranked severity and, in some cases, frequency.

2.5. Adverse events categories

Side effects to ketamine were classified as acute-time limited or prolonged. Acute-time limited reactions, such as dizziness or burning sensation in the nose, occurred during IN administration and generally abated over a 15–120 min period. Potential long-term side effects from ketamine use included: (i) torso acne, (ii) problems with urination, (iii) sustained loss in sensory perception, or (iv) other medical concerns the patient thought might be associated with ketamine.

2.6. Statistical analyses

2.6.1. Data reduction

Principal component analysis (PCA) with oblimin rotation was used as a data reduction tool that combined the 49 Likert-rated survey items into four composite oblique symptom clusters. Oblimin was selected over more conventional rotational strategies (e.g., varimax) as it does not force the components to be uncorrelated, as this is an unreasonable assumption with symptom scores. Symptoms were also categorized as either unique to FOH phenotype (e.g., thermal insensitivity), diagnostic for BPD (e.g., high energy - pressured speech - racing thoughts) or strongly associated with FOH as well as other subtypes of BPD (e.g., physical aggression) based on consensus ratings from two psychiatrists (DFP, MHT).

2.6.2. Within subject response

Paired *t*-tests were used to assess within subject differences in pre-treatment versus post-treatment symptom ratings on the four composite ratings. Within subject effect size measures and 95% confidence intervals were computed using procedure developed by Gibbons et al. (1993), (implemented in the R package '*effsize*'), which provides numerically equivalent results to Dunlap et al. (1996).

2.6.3. Tolerance

Paired *t*-tests were also used to test for development of tolerance to side-effects of InK by comparing side-effect ratings at the time InK was initiated to current side-effect ratings. Further, non-linear mixed effects

models (R package *'nlme'*) were used to evaluate the tolerance time course for the most frequent acute-time limited reactions, which were the most suitable for modeling. Independent *t*-test was used to compare subjects continuing InK treatment from subjects who discontinued use in age of onset, peak dosage and duration of treatment.

3. Results

3.1. Sample

Of the sixty cases invited to respond to the survey, fifty-one (85%) responded to the invitation. Of these, 45 patients (75% of sample, 25% female) completed the survey. 40 patients (89%) continued to receive InK treatment at the time of survey ("continuers") while 5 patients (11%) had discontinued InK treatment ("non-continuers"). The mean age of the sample was 15 ± 6.7 years. The youngest was 6 years of age the eldest was 37.

3.2. Dosing

The survey respondents initiated treatment with InK at 15.9 ± 6.7 years of age (mean and SD) and, on average, received treatment for 1.71 ± 1.36 years. Mean ketamine dosage (current or at time of discontinuation) was 165 ± 75 mg, (range 20–360 mg) administered once every 2–5 (mean 3.0 ± 0.6) days. Five of the 45 patients discontinued treatment with InK; 3 considered the treatment ineffective, 1 discontinued due to family circumstances, including disagreement over treatment/finances, and 1 found treatment was inconvenient in his new college setting. Comparisons between subjects continuing versus discontinuing ketamine on age of initiation (15.6 ± 6.7 vs 18.5 ± 5.8 years), average dosage (173 ± 40 vs 165 ± 78 mg) and duration of treatment (1.81 ± 1.39 vs 0.88 ± 0.62 years) were not significantly different within this limited sample.

3.3. Effectiveness

3.3.1. Chart review

Concordance in CGI scores between the two raters was high ($r = 0.897$, $p < 10^{-15}$) for the 39 complete charts available for review. Prior to initiation of InK the patients were seen as severely ill (CGIs = 5.7 ± 0.7), with 10 of the patients rated as "amongst the most severely ill" by at least one of the two raters. At endpoint, following addition of InK into their treatment regimen, and months of adjustment and optimization, patients were typically rated as mildly ill (CGIs = 3.2 ± 1.1) with a 2.55-point drop in scores ($t_{38} = -14.21$, $p < 10^{-15}$). Mean improvement on the CGIi was 1.9 ± 0.9. Eight patients were seen as very much improved by both raters, 26 were much improved and only 5 patients were mildly improved or unchanged. None were consistently viewed as worsened. A typical pattern was for the subject to have such severe psychopathology prior to initiation of ketamine that they were unable to attend school and were home schooled to the extent possible. They were also physically aggressive towards parents or siblings, had no friends to speak of and were on several different psychiatric medications. After initiation and titration of InK they were often attending regular school, had ceased fighting with parents, were making friends and were on a simpler drug regimen. Breakthrough symptoms were sometimes seen however on the day prior to the next dose or when the ambient temperature was excessively high. There were no age-related differences in effectiveness ($p > 0.4$),

3.3.2. Survey results – symptom scores

Principal component analysis (PCA) with oblimin rotation was used to reduce the Likert-like symptom items into rotated orthogonal components (Table 1). Four components were selected as recommended by the Velicer Minimum Average Partial (MAP) test criterion (Velicer, 1976; Zwick and Velicer, 1986). These four components accounted for

Table 1
Data reduction using principal component analysis with oblimin rotation to reduce 49 symptom scores into four oblique components.

Clinical Symptoms	TC1	TC3	TC4	TC2	Category
Fearful new challenges, situations	**0.86**	–	−0.10	–	FOH
Devalues self or others	**0.86**	–	–	−0.12	BPD
Easily shamed or humiliated	**0.85**	−0.18	–	–	FOH
Fearful of separation	**0.74**	0.16	–	–	FOH
Abrupt mood swings	**0.71**	0.17	0.20	–	Both not core
Low energy, lack of motivation	**0.71**	–	–	0.10	BPD
Suicidal ideation or planning	**0.66**	–	0.18	−0.26	BPD
Difficulty sleep initiation or maintenance	**0.66**	0.10	0.14	–	Both not core
Difficulty initiating actions	**0.63**	0.26	−0.18	–	Both not core
Fearful of injury / accident	**0.62**	–	0.22	0.14	FOH
Hypersexuality	**0.61**	−0.40	0.23	0.10	BPD
Misperceives limit setting as threat	**0.60**	0.34	–	0.13	FOH
Avoidance of tasks	**0.59**	0.36	–	–	Both not core
Social withdrawal	**0.56**	0.26	−0.21	0.14	BPD
Misperceives neutral situations as threat	**0.55**	–	0.30	–	FOH
Sensitive to heat	**0.55**	0.28	0.11	–	FOH
Sensitive to cold	**0.51**	−0.49	–	–	FOH
Irrational fears (ghosts, monsters)	**0.49**	0.20	0.14	0.28	FOH
Highly vigilant, easily startled	**0.49**	0.15	0.27	–	FOH
Unrealistic expectations	**0.49**	0.36	–	–	BPD
Irritability	**0.48**	0.44	0.11	–	BPD
Perfectionistic worries	**0.48**	–	0.31	–	FOH
Nightmares	**0.47**	–	0.37	0.26	FOH
Aggressive thoughts	**0.43**	0.20	0.42	–	Both not core
Excitability, pressured speech, racing thoughts	**0.41**	0.20	0.34	–	BPD
Physical aggression to parents severity	–	**0.85**	0.11	–	Both not core
Physical aggression to parents frequency	–	**0.77**	0.19	–	Both not core
Physical aggression to sibs frequency	−0.12	**0.72**	–	0.19	Both not core
Oppositionality	0.34	**0.67**	−0.11	–	Both not core
Strong unyielding drive	0.23	**0.63**	–	0.12	FOH
Physical aggression property severity	–	**0.62**	0.35	–	Both not core
Verbal aggression	0.29	**0.61**	0.16	−0.13	Both not core
Physical aggression property frequency	–	**0.60**	0.44	–	Both not core
Physical aggression to sibs severity	0.12	**0.59**	−0.10	0.14	Both not core
Deflection of blame	0.39	**0.55**	–	0.10	Both not core
Inflexibility	0.46	**0.54**	–	–	Both not core
Impulsivity	0.41	**0.50**	–	0.15	BPD
Difficulty concentrating / distractability	0.32	**0.41**	–	0.20	BPD
Sensory sensitivity	0.35	**0.37**	−0.10	0.21	FOH
Physical aggression non-family frequency	−0.10	–	**0.67**	0.40	Both not core
Physical aggression self frequency	0.16	0.13	**0.62**	–	Both not core
Physical aggression self severity	0.18	0.16	**0.61**	−0.14	Both not core
Physical aggression non-family severity	–	0.16	**0.56**	0.24	Both not core
Suicide attempts	–	0.14	**0.53**	−0.24	BPD
Hallucinations / psychosis	0.26	–	**0.38**	0.21	Both not core
Physical aggression animals severity	0.10	–	–	**0.87**	Both not core
Physical aggression animals frequency	–	–	0.14	**0.84**	Both not core
Psychomotor retardation	–	0.10	−0.40	**0.70**	BPD
Other sleep disturbance	–	0.18	0.27	**0.54**	FOH

62.2% of the variance in the individual item ratings. Items with high loadings on the first component involved fear, low self-esteem, suicidal ideation, mood swings and low energy. Items with high loading on the second component reflected aggression towards parents, siblings and property, oppositionality and irritability. Items with strong loading on the third component involved aggression towards self, non-family members and suicide attempts. Items loading onto the fourth component included aggression towards animals, psychomotor retardation and sleep disturbances.

Overall, there were highly significant within subject differences in pretreatment versus post-treatment ratings. Reduction in scores on component 1 following ketamine titration was associated with a very large effect size (Cohen's d = 2.92, 95% CI 2.27–3.57, t_{39} = 14.9, $p < 10^{-16}$). Similarly, there were also a large pre-post ketamine differences in component 2 (d = 1.71, 95% CI 1.19–2.24, t_{39} = 10.70, $p < 10^{-12}$) and component 3 (d = 1.10, 95% CI 0.616–1.58, t_{39} = 5.82, $p < 10^{-6}$). There was a moderate pre-post ketamine difference on component 4 (d = 0.626, 95% CI 0.164–1.09, t_{39} = 3.63, p = 0.0008). Based on 95% confidence intervals Component 1 showed a greater pre-post difference than any of the other components. Component 2 also showed a greater pre-post difference than Component 4. Twelve of the 15 symptoms unique to the FOH phenotype loaded onto Component 1.

Other useful information gleaned from the survey was that 21 of the 40 continuers (52.5%) had one or more psychiatric hospitalizations prior to initiation of ketamine. None of the continuers had a psychiatric hospitalization after ketamine was initiated. Those with prior hospitalizations had no subsequent hospitalizations during a 2.1 ± 0.6 year post initiation of ketamine follow up period. Table 2 summarizes data on changes in medication treatment after initiation of ketamine. There were 41 instances in which antipsychotics were reduced or eliminated. Mood stabilizers, antidepressants and anxiolytics were reduced or eliminated in 25, 11 and 7 subjects, respectively. Following initiation of ketamine 3 subjects were prescribed oxcarbazepine, 2 clonidine, 1 trazodone and 1 mixed amphetamine salts. Concomitant psychotropic medications were discontinued in 43% of continuous users. The remainder received from 1 to 3 additional medications (mean 1.6 ± 0.7), typically a low dose of an antipsychotic, mood stabilizer or clonidine.

Table 2
Number of subjects in whom specific medications were decreased, eliminated or added after initiation of ketamine.

	Decreased	Eliminated	Added
Antipsychotics			
aripiprazole	4	9	
asenapine		1	
clozapine	1		
fluphenazine	1		
olanzapine		1	
quetiapine	3	4	
risperidone	5	10	
ziprasidone	2	2	
Mood Stabilizers			
lamotrigine		7	
lithium	3	5	
oxcarbazepine	2	1	3
topiramate		1	
valproate	2	4	
Antidepressants			
duloxetine		1	
escitalopram		2	
fluoxetine		1	
fluvoxamine		1	
nortryptiline		1	
sertraline		3	
trazodone		1	1
venlafaxine		1	
Anxiolytics			
clonazepam	1	5	
lorazepam		1	
Others			
modafinil	1		
benztropine		2	
clonidine	1	1	2
guanfacine		1	
propranolol		1	
psychostimulants	1	2	1

3.3.3. Content analysis

Thirty-nine open ended written reports on how INK affected the life of the patients were provided by parents or older patients, and codified using content analysis. Clinical global impressions derived from these reports identified 3 patients as minimally improved, 11 as much improved and 25 as very much improved for an average CGI improvement score of 1.44 (95% CI 1.23–1.64). Information on academics or work performance was provided for 21 cases. One family reported no change, 7 were much improved and 13 very much improved in their ability to attend or perform. It was noted in 24/24 reports that the patient was easier to get along with and in 24/24 cases that family life had improved. Patients were noted to be less confrontational in 22/23 reports, less angry in 21/22, less fearful in 24/26, less depressed in 25/27, engaging in more activities in 24/26 and sleeping better in 6/6. In 12/13 reports an improvement was noted in ability to make friends, and in 14/14 there was an improvement in ability to socialize.

3.4. Safety

3.4.1. Acute-time limited reactions

Fourteen potential acute-time limited reactions (ATLRs) were observed (see Table 3). The most commonly reported ATLR was “a sense of relaxation calm and bodily warmth” reported in over half of the patients as lasting for 40 min or longer. A large majority (88%) of this group reported that experience to be enjoyable. The most frequently reported negative short-term side-effects were dizziness (84.4%), wobbly gait (73.3%), and stinging sensation in the nose (71.1%). Of these, most were reported to be of relatively brief duration (< 20 min). Once therapeutic doses were achieved, the experience of dizziness, wobbly gait and stinging in nose were reported as present but reduced in intensity. Significant alterations in severity, frequency and duration for the most common ATLRs at therapeutic dose (affecting $\geq$ 10 subjects) are indicated on Table 3. There were no age-related differences in severity of common side effects (e.g., burning nose, elation, sleepiness, heaviness in limbs) in those reporting these side effects, except for diziness, which was less severe in older individuals ($r = -0.65$, $p < 0.02$)

The ATLRs that showed the most significant reduction with continued treatment, and which affected the greatest number of subjects, were dizziness and wobbly gait. Non-linear mixed effects analyses fitting to a 4-parameter logistic time course equation were used to estimate time to half-maximal reduction in severity for these two ATLRs. For dizziness there was a relatively rapid decline in severity (time to half-maximal was 0.20 years, 95% CI 0.05–0.35 years, $F_{1,19}$ = 7.43, $p < 0.02$). In contrast wobbly gait / loss of coordination took substantially longer to diminish (time to half-maximal was 1.17 years, 95% CI 1.01–1.33 years, $F_{1,20}$ = 15.04, $p < 10^{-16}$). The decrement in severity occurred despite the fact that later doses were almost universally greater than doses administered at the initiation of treatment.

3.4.2. Persistent adverse events

Two patients reported persistent sensory changes. One subject reported loss of temperature sensation in all areas of his body except for the tongue. Neurological exam found gamma neuron loss at the level of the spinal cord, determined not to be progressive. The second patient experienced numbness in their upper extremities (fingers to mid-arms) when ambient temperature increased above 80 °F and when exposed to a warm shower. Neurological exam concluded that this was not a progressive deficit. In both cases, family and patient elected to continue

Table 3
Acute-time limited reactions immediately following intranasal ketamine administration.

Symptoms	Subjects experiencing it with some regularity initially or at therapeutic dose	Subjects experiencing it with some regularity at therapeutic dose	Ratings of severity, frequency, duration and nature in subjects experiencing symptoms at therapeutic dose				
			Period	Severity[a]	Frequency[b]	Duration[c]	Nature[d]
Sense of Calm or Relaxation[e]	39 (86.7%)	34 (75.6%)	Initial	2.2 ± 0.9	2.8 ± 0.9	51 ± 28	0, 4, 30
			Current	2.1 ± 0.7	2.9 ± 0.9	49 ± 31	
Dizziness[e]	38 (84.4%)	24 (53.3%)	Initial	2.3 ± 0.9	3.3 ± 0.9	26 ± 19	6, 16, 2
			Current	1.5 ± 0.7[§]	2.7 ± 1.1[¥]	17 ± 16[†]	
Wobbly Gait/Loss of Coordination[e]	33 (73.3%)	25 (55.6%)	Initial	2.0 ± 0.8	2.8 ± 1.1	30 ± 24	2, 21, 2
			Current	1.5 ± 0.3[¥]	2.0 ± 1.1[**]	17 ± 16[¥]	
Nasal Burning or Stinging[e]	32 (71.1%)	17 (37.8%)	Initial	2.4 ± 0.8	3.1 ± 0.8	12 ± 18	11, 6, 0
			Current	1.8 ± 0.9[**]	2.4 ± 1.2[**]	8 ± 7	
Sensory Distortions[e]	24 (53.3%)	16 (35.6%)	Initial	2.1 ± 0.9	2.6 ± 0.9	23 ± 17	4, 6, 6
			Current	1.6 ± 0.6[*]	1.6 ± 0.8[**]	16 ± 19[**]	
Elated, Silly or Giddy Feeling[e]	24 (53.3%)	10 (22.2%)	Initial	2.2 ± 1.0	2.6 ± 1.1	31 ± 19	2, 1, 7
			Current	1.5 ± 0.5	2.1 ± 1.1	23 ± 23[*]	
Sleepy, Tired or Fatigued[e]	23 (51.1%)	13 (28.9%)	Initial	2.3 ± 0.9	2.7 ± 1.0	46 ± 27	4, 8, 2
			Current	1.7 ± 0.6[*]	2.1 ± 1.0[*]	38 ± 29	
Head or Limbs Heavy or Light	22 (48.9%)	7 (15.6%)	Initial	2.0 ± 0.8	2.4 ± 1.0	15 ± 11	1, 6, 0
			Current	1.1 ± 0.4	1.4 ± 0.5	9 ± 5	
Warmth or Cold Sensations	18 (40.0%)	9 (20.0%)	Initial	2.0 ± 0.9	2.3 ± 1.1	31 ± 29	0, 6, 3
			Current	2.0 ± 0.7	2.4 ± 1.2	29 ± 30	
Distorted Sense of Time	16 (35.6%)	7 (15.6%)	Initial	2.4 ± 1.0	3.0 ± 1.0	36 ± 31	2, 4, 1
			Current	1.3 ± 0.5	1.9 ± 0.9	24 ± 26	
Nausea	12 (26.7%)	4 (8.9%)	Initial	2.3 ± 1.5	2.0 ± 0.8	45 ± 41	4, 0, 0
			Current	3.0 ± 0.8	2.3 ± 0.5	48 ± 38	
Numbness	10 (22.2%)	7 (15.6%)	Initial	1.9 ± 1.1	2.4 ± 1.3	28 ± 21	2, 4, 1
			Current	1.3 ± 0.5	2.0 ± 1.4	28 ± 16	
Outside of Body	10 (22.2%)	6 (13.3%)	Initial	2.3 ± 1.0	2.7 ± 1.2	42 ± 30	1, 2, 3
			Current	1.8 ± 0.8	2.2 ± 1.0	38 ± 34	
Sweating on the Hands or Feet	7 (15.6%)	5 (11.1%)	Initial	1.6 ± 0.9	2.0 ± 1.0	22 ± 33	1, 4, 0
			Current	1.6 ± 0.9	1.8 ± 1.1	22 ± 33	

[a] Severity: 1 = mild, 2 = moderate, 3 = strong, 4 = severe.
[b] Frequency: 1 = infrequent, 2 = frequent, 3 = almost always, 4 = always.
[c] Duration: minutes.
[d] Nature: distressing/unpleasant, neutral, enjoyable/pleasant.
[e] Initial versus current ratings with n > 10 on therapeutic dose.
* $p < 0.05$.
** $p < 0.01$.
¥ $p < 0.001$.
† $p < 0.0001$.
§ $p < 10^{-5}$.

ketamine because of the significant benefits that had accrued from treatment. Additional persistent AEs included urination problems in 5 patients (11.1%) and torso acne in 4 patients (8.9%).

3.4.3. Substance abuse

One potential concern with ketamine is that it might serve as a gateway drug and lead patients to use other psychoactive substances. Hence, degree of alcohol and drug use prior to initiation with ketamine was compared to degree of use during ketamine treatment. As seen in Table 4, there was no increase in use. Rather, there were trend level decreases in frequency of alcohol and marijuana use while receiving IN ketamine.

4. Discussion

This retrospective chart review and survey of the off-label longitudinal use of InK in 45 youth with refractory BD-FOH provides preliminary support for the potential effectiveness and tolerability of this treatment in clinical practice. The data presented are preliminary, neither blind nor placebo-controlled, and must be interpreted with caution. Nevertheless, the results of this case series are consistent with earlier reports of the efficacy and safety of ketamine administered by intranasal instillation to 12 BD-FOH youth over a 2-month period.

Patients were treated for 3 mos. – 6.5 years. Peak InK doses ranged from 20 to 360 mg per administration, and attenuated symptoms of BD/FOH for variable periods of time, typically 2–5 days. Clinically significant benefits were often apparent after the first treatment. Analysis of patient charts and written impressions revealed a substantial improvement in CGI severity scores with most patients who continued on ketamine rated as much to very much improved. Principal component analysis was used to reduce individual symptom scores into 4 components. All components were significantly reduced by ketamine, with components 1 and 2 showing the largest therapeutic effect sizes. Twelve of the 15 unique FOH symptoms loaded onto component 1. Component 2 consisted primarily of aggressive and oppositional symptoms common to both FOH as well as other subtypes of bipolar disorder. As all the subjects had the FOH subtype of bipolar disorder it is unclear how beneficial ketamine might be in bipolar patients who do not have the FOH subtype.

CGI analyses of surveys and patient records following ketamine were supported by observations regarding risk for psychiatric hospitalization. More than half of the subjects who continued to receive

Table 4
Average days per month of alcohol, marijuana and other psychoactive substance use prior to and following initiation of ketamine treatment.

	Before mean {95%CI}	After mean {95% CI}	*t*-test	df	p value
Alcohol	1.85 {0.07–3.62}	0.36 {−0.08–0.80}	1.91	38	< 0.07
Marijuana	2.05 {0.11–3.99}	0.30 {−0.12–0.72}	1.76	39	< 0.09
Other drugs	1.69 {−1.62–5.00}	1.54 {−1.79–4.86}	0.07	12	> 0.9

ketamine had at least one psychiatric hospitalization in the year preceding initiation of ketamine. Indeed, this may have been a precipitant to seeking out or agreeing to try a course of IN ketamine. None of these individuals were hospitalized during the ca 2-year period following initiation of ketamine. If this preliminary finding is confirmed in treatment trials it would suggest that InK ketamine may be a very cost effective treatment.

Most acute-time limited reactions occurred specifically during administration and persisted for 15–120 min. The intensity, frequency and duration of these reactions tended to gradually decrease with repeated administrations without loss in efficacy. Interestingly, tolerance did not appear to develop to the most pleasurable ATLR, which was a sense of relaxation, calm or warmth. At the onset of treatment drug and alcohol abuse was not a significant factor and did not increase even as the patients matured during the study.

Long term AEs were limited and relatively rare, but, in a few cases were of a severe nature, (loss of temperature sensation over most or part of the body) but not progressive. Earlier reports indicated that the most common AE associated with ketamine abuse was ulcerative cystitis, which was reported to occur in 15–20% of chronic users (Jalil and Gupta, 2012), In the present sample a self-limiting (non-ulcerative) cystitis was reported to occur in 5 individuals. Complaints were of pain on urination. These side-effects were non-persistent or intermittent. All urinalyses in these patients were WNL. One patient experienced numbness of hands and forearms when exposed to high ambient temperature (above 80 °F, or when exposed to a warm shower). This condition was found to not be progressive, and could not be conclusively attributed to ketamine treatment.

Ketamine was generally titrated over a number of weeks until an effective dose was reached that resulted in marked attenuation or remission of symptoms. Clinically significant benefits were often apparent after the first treatment. These benefits persisted with only minor subsequent dose adjustments in most cases. The most common initial breakthrough symptom was difficulty thermoregulating, typically, overheating at night prior to sleep resulting in arousal disorders of sleep. Other than the acute-time limited reactions during the administration period most subjects experienced no side effects during the typically 2–5 day period between doses. Following titration it was usually possible to eliminate or reduce many of the other medications patients were receiving. This was particularly true for antipsychotic medications and mood stabilizers. Most patients however received 1–3 concomitant medications.

Finally, a deficit in thermoregulation appears to be tightly linked to symptoms of BP-FOH, and thermoregulatory deficits are known to disrupt sleep-onset, sleep offset and are associated with arousal disorders of sleep. Thus, it was interesting that one apparent conclusion from the chart review was that heat sensitivity and cold tolerance were two key target symptoms useful for dose titration and for determining an appropriate time period between ketamine treatment cycles.

Neuropharmacologically, the diverse array of symptoms seen in youths with BD-FOH including fear of harm, territorial aggression, arousal disorders of sleep, deficient thermoregulation and more classic symptoms of mania may result from dysregulation of the oxerigenic system. Orexins are neuropeptide transmitters whose cell bodies reside in the lateral, dorsomedial and perifornical hypothalamus (Nambu et al., 1999; Richardson and Aston-Jones, 2012), densely innervate all portions of the hypothalamus (e.g., ventrolateral preoptic area, suprachiasmatic nucleus) and have primary projections to cell bodies for the noradrenergic, serotonergic, dopaminergic, histaminergic and cholinergic systems in the locus coeruleus, raphe nuclei, ventral tegmental area, tuberomamillary nucleus and laterodorsal and pedunculopontine nuclei, respectively (Alexandre et al., 2013; Emeson and Morabito, 2005; Nambu et al., 1999; Richardson and Aston-Jones, 2012). The orexin system also has widespread projection to amygdala, hippocampus, septal area and neocortex. Overall, this system appears to play a critical role in wakefulness, arousal, sleep and circadian rhythms (Alexandre et al., 2013), thermoregulation and energy balance (Nattie and Li, 2012), stress response (Nattie and Li, 2012), panic and anxiety (Johnson et al., 2012), reward processing (Richardson and Aston-Jones, 2012), fear conditioning (Wang et al., 2017), feeding behavior (Nambu et al., 1999) and defensive flight or flight reactions (Kayaba et al., 2003). Loss or hypofunction of orexin neurons is associated with narcolepsy (Alexandre et al., 2013) Conversely, we propose that overactivation or dysregulation of portions of the orexin system may be responsible for FOH.

There are several ways in which ketamine may act to either modulate the orexin system or overcome effects of excessive stimulation. First, ketamine, as an NMDA receptor antagonist, should be able to directly attenuate the effects of orexin (Peever et al., 2003; Tose et al., 2009). Second, orexin-mediated fear conditioning may be reversed through normalization of BDNF gene methylation that can be brought about via long-term ketamine use (Ju et al., 2017). In animal studies, ketamine has been found to increase BDNF gene expression that results in an increase in resilience to stress (Duman and Agajanian, 2014). BDNF also plays a critical role in thermoregulation. A recently described facet in the orchestration of the homeostatic response to heat are warm sensitive neurons within the preoptic area that have been molecularly defined by the co-expression of the neuropeptides BDNF and pituitary cyclase activating peptide (PCAP) (Tan et al., 2016). Taken together, we believe these findings support the idea that ketamine's actions on BDNF gene induction through orexigenic transmission has multiple salutory effects in the FOH phenotype; to improve thermoregulatory responses to the environment and to stressors, as well as in the reduction of fear sensitization.

5. Limitations

The limitations of this study include a small sample size that was drawn from a single private practice, as well as those of any retrospective study that employs survey data and recall of severity of symptoms. In particular, contemporaneous data on the patient's clinical state prior to initiation of ketamine was available in the chart review. The survey, in contrast, asked subjects or parents to recall how the subject was prior to initiation of ketamine, so impressions may be filtered or amplified by the contrast. Response to survey was incomplete (45 of 60 responded), possibly leading to bias towards survey response from patients who responded positively to treatment.

Another concern is that some of the patients were referred to DFP for treatment with ketamine and may have benefited from DFP's particular expertise in treating youths with BD-FOH. However, most of the patients had been treated with traditional agents by DFP prior to ketamine without significant improvement. Carefully designed trials will need to be conducted. Further research should focus on the spectrum of type of patients that will benefit from ketamine use, as well as the long-term sequelae of ketamine treatment.

Disclosures

Dr. Teicher receives consulting fees and royalties from BioBehavioral Diagnostic Company/Pearson as inventor of the Quotient ADHD System through a licensing agreement with McLean Hospital. Dr. Teicher holds nine patients related to the diagnosis of psychiatric disorders and six patents related to the treatment of ADHD or depression. None of these involve ketamine. Dr. Teicher has recently commenced a consulting relationship with Abide Therapeutics.

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Research report

Fear of harm, a possible phenotype of pediatric bipolar disorder: A dimensional approach to diagnosis for genotyping psychiatric syndromes

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ABSTRACT

Background: In a prior concordance study of affected sibling pairs with a community diagnosis of pediatric bipolar disorder (PBD) a behavioral phenotype termed Fear of Harm (FOH) was found to have one of the strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs [Papolos, D., Hennen, J., Cockerham, M.S, Lachman, H., 2007]. A strategy for identifying phenotypic subtypes: concordance of symptom dimensions between sibling pairs who met screening criteria for a genetic linkage study of childhood-onset bipolar disorder using the Child Bipolar Questionnaire (CBQ) was employed. J. Affect. Disord. 99, 27–36.]. We used the *Child Bipolar Questionnaire* (OUT) (CBQ) to further elucidate this behavioral phenotype of PBD. We hypothesized that selective factors including parent reported symptoms of mania and depression, would be distinguishing features of impairment between groups defined by 1) the magnitude of their score on a continuous measure of FOH, and 2) the high FOH group would have significantly greater levels of severity on course of illness variables. These measures included earlier age of onset of first psychiatric symptoms, first hospitalization, and frequency of psychiatric hospitalizations, as well as, degree of social impairment as determined by exposure to the juvenile justice system and school performance problems.
Methods: The sample was comprised of children with community diagnoses of bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BPD ($N=5335$). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always. This group was divided randomly into two groups, the exploratory group ($N=2668$) and the hypothesis testing (study) group ($N=2666$). The exploratory group was used for the development of hypotheses and the study group was used to test these hypotheses on a new set of data. All results reported here derive from the latter group. In subsequent analyses, we classified each child as having a high degree of FOH, low FOH, or no FOH. We examined a subset of the sample for differences in age of onset of first psychiatric symptoms, course of illness and measures of symptom severity. These groups were compared using the chi-square procedure for categorical data and the Analysis of Variance (ANOVA) with Scheffe pair wise tests for continuous variables. The Child Bipolar Questionnaire V.2.0, the Yale-Brown Obsessive Compulsive Scale (YBOCS) and the Overt Aggression Scale (OAS) were the principal instruments used to obtain diagnostic information for this study.
Results: We found that children representative of the FOH phenotype when compared to children with PBD who lack this trait had higher indices of severity of mania and depression, as well as other

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indices that reflect severity and course of illness. Trait factors were derived from a factor analysis of CBQ in a large population of children diagnosed with or at risk for PBD, and used to further elucidate trait features of children with FOH. Children with the FOH traits were also more likely to be defined by six CBQ factors; Sleep/Arousal, Harm to Self and Others, Territorial Aggression, Anxiety, Self-esteem, Psychosis/Parasomnias/Sweet Cravings/Obsessions (PPSO).
Limitations: This data is derived from samples enriched with bipolar disorder cases. Further validation is needed with samples in which childhood-onset BD is rarer and diagnoses more diverse. Clinician diagnosis was not validated via research interview.
Conclusions: The FOH phenotype, as defined by a metric derived from combining items from the YBOCS/OAS, is a clinically homogeneous behavioral phenotype of PBD with early age of onset, severe manic and depressive symptoms, and significant social impairment that is strongly associated with 6 CBQ factors and can be easily identified using the CBQ. Through the examination of dimensional features of PBD in an enriched sample of large size, we were able to further refine a phenotype and identify clinical dimensions potentially linked to endophenotypic markers that may prove fruitful in differential diagnosis, treatment and etiological studies of PBD. The nature of the sets of specific symptoms that comprise the FOH factors enabled us to propose a biological model *for the phenotype* (OUT) that involves a complex orexigenic circuit which links hypothalamic, limbic, and other brain nuclei primarily responsible for the regulation of behavioral and proposed physiological features of the FOH phenotype.

1. Introduction

There is a general agreement within the clinical and research communities that the field of psychiatry is in a state of flux as advances in neuroscience, neuroimaging and genetics begin to challenge many of its current theoretical underpinnings, particularly those related to the definition and causation of mental disorders (Kendell and Jablensky, 2003; Charney et al., 2002). It is becoming increasingly apparent that the broad and imprecise nature of the current psychiatric diagnostic constructs is a limiting factor in the development of reproducible genetic and imaging research and in our understanding of the genetic basis of human behavioral abnormalities.

Recent findings from clinical studies have led some clinical investigators to conclude that psychiatric diagnosis such as obsessive–compulsive disorder and bipolar II disorder would be better conceptualized as a spectrum of overlapping syndromes (Hantouche and Akiskal, 2006) or much more well defined (Mataix-Cols et al., 2005; Leckman et al., 2007) than found in unitary nosologic entities as currently promulgated in DSM-IV. These studies are consistent with the idea that psychiatric syndromes may be better defined by an ordered matrix of symptom clusters or behavioral dimensions than by a set of discrete categories (Gusnard et al., 2003; Smoller et al., 2008). While categorical definitions tend to obscure symptoms not central to the construct of a particular disorder, i.e., the DSM-IV caveat, "Do not include if better accounted for by another disorder", clusters of individual symptoms that overlap with currently established diagnostic boundaries may define more homogeneous phenotypic subtypes for genetic studies. Future pharmacological treatments like CRF and NPY inhibitors and agonists and circadian interventions, such as sleep deprivation or full spectrum light for depression, that target specific functional systems in the brain will require a more differentiated classification of the clinical populations selected for treatment than the approaches that are currently available (Mathew et al., 2008; Ehlers et al., 1997; Robison et al., 2004; Zhou et al., 2008; Xapelli et al., 2006; Silva et al., 2005; Kishi and Elmquist, 2005; Benedetti et al., 2007; Kehne, 2007).

Smoller and Tsuang (1998) have suggested that the success of psychiatric genetics may require the development of a genetic nosology that can classify individuals in terms of the heritable aspects of psychopathology. Fruitful endophenotype studies depend on the selection of heritable, quantitative traits that can be objectively and reliably measured. However, to date, there are no agreed upon methods by which candidate behavioral phenotypes can be chosen and applied (Bearden and Freimer, 2006; van Praag, 1993). An important dividend from an effort to define the boundaries of heritable phenotypes for genetic studies would be a refinement in the nosology of psychiatric conditions (Smoller and Tsuang, 1998; Kendell and Jablensky, 2003; Finegan, 1998).

Clearly, in psychiatry, the goal over the next decade will be to establish behavioral phenotypes strongly associated with biologically based anchor endophenotypes that respond to specific pharmacological or circadian treatments (Drevets et al., 2006). This need is no more critical than in the area of pediatric bipolar disorder (PBD) as there is no current consensus in the field about diagnosis. A recent study reports that the estimated annual number of youth office-based visits with a diagnosis of bipolar disorder in the US increased from 25 (1994–1995) to 1003 (2002–2003) visits per 100,000 population — a 40-fold rise (Moreno et al., 2007). Though several phenotypes have been proposed (Geller and Tillman, 2005; Leibenluft et al., 2003; Papolos, 2003; Biederman et al., 2004), there remains some controversy about how the illness is diagnosed in childhood. Regardless of the differences between research groups regarding how bipolar disorder in children is defined, it is agreed that PBD is a serious and pernicious illness. With early intervention during the period of time in which youths are exhibiting subsyndromal symptoms of PBD, it appears that the progression of the illness to the more malignant manifestation of the disorder may be avoided (Demeter et al., 2008; Holtmann et al., 2008; Geller and Tillman, 2005; Craney and Geller, 2003; Biederman et al., 2000; Dilsaver, 2001; Kim and Miklowitz, 2002; Schapiro, 2005; Youngstrom et al., 2005).

Two parallel but separate traditions have sought to define behavioral phenotypes: the first, more closely identified with clinical psychiatry, has utilized categorical diagnoses (e.g., bipolar disorder, obsessive–compulsive disorder, panic disorder and social phobia) that sharply delineate sets of psychiatric symptoms into putatively non-overlapping diagnoses. The other, more closely identified with psychological studies of personality development, has examined dimensional traits (e.g., approach/avoidance, neuroticism and anxious temperament, behavioral inhibition, self-directedness, persistence, novelty seeking, reward dependence, fear of harm, Brown et al., 1992; Eysenck, 1997; Papolos et al., 2006; De Fruyt et al., 2006; Gusnard et al., 2003). A genetic nosology of bipolar disorder could incorporate features of both traditions to provide a strategy for optimizing genetic approaches to bipolar disorder (BPD). We have attempted to do that in this study.

By systematically selecting features of a disorder that might result from distinct genetic influences, and by carefully defining the target phenotype, we can hope to narrow the range of genes that influence risk for the trait in a study population, thereby increasing the likelihood of finding them. We have taken an approach that we believe gives us the best opportunity to determine the genetic associates of PBD. We ascertained cases of early onset PBD from families with multiple first degree relatives diagnosed with BPD and determined heritability factors by performing concordance studies on affected sibling pairs and twins.

In genomics, the importance of the analysis of symptom dimensions as a strategy for genotyping is becoming more evident. Cheng et al. (2006) used both standard diagnostic models and the comorbid symptoms of psychosis, suicidal behavior and panic disorder to identify phenotypic subtypes for a genome-wide linkage scan in a large bipolar sample. Over half the regions implicated by the strongest linkage signals (genome-wide significance) were identified using phenotypic subtypes. Cheng and colleagues concluded that a dissection of the disease phenotype can enrich the harvest of linkage signals and expedite the search for susceptibility genes. In a genetic study of BPD pedigrees ascertained through adult probands, Faraone et al. (2006) quantified dimensions of BPD symptoms derived from a principal component factor analysis, determined their heritability, and used the heritable factors in a variance-components linkage analysis.

Using a similar methodology, we found that a behavioral dimension that encompasses aggressive obsessions and aggressive behavior directed towards others and self defined as Fear of Harm (FOH) had one of the strongest concordance coefficients (rho) between probands and siblings compared with age and sex matched singletons, and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs (Papolos et al., 2007). In the present study, we sought to further examine this behavioral phenotype defined by a metric adopted from the YBOCS and OAS, well-standardized scales that measure obsessive–compulsive and aggressive behaviors. We hypothesized that selective factors including mania and depression, would be distinguishing features of impairment between groups defined by the magnitude of their score on a continuous measure of FOH. Additionally, we hypothesized that parent-reported symptom severity as measured by earlier age of onset of first psychiatric symptoms, first hospitalization, and frequency of psychiatric hospitalizations, as well as, degree of social impairment, as determined by exposure to the juvenile justice system and school performance problems, would be greater in the high FOH phenotype group when compared to the low or no FOH group.

This potentially heritable behavioral dimension or trait feature of FOH overlaps with DSM-IV definitions of bipolar disorder, obsessive–compulsive and other anxiety disorders, oppositional defiant, conduct disorder and impulse-control disorder, as well as, parasomnias and REM sleep behavior disorder with symptoms of suicidality and psychosis. Thus, the trait FOH, does not pertain to any specific set of current DSM-IV criteria and, therefore, cannot be diagnosed using the categorical nosology promulgated by DSM-IV.

2. Methods

The sample was comprised of children with community diagnoses of bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BPD ($N=5335$). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always. This group was divided randomly into two groups, the exploratory group ($N=2668$) and the study group ($N=2666$). The exploratory group was used for exploratory data analysis and the development of hypotheses. A study group was used to test these hypotheses using a new and uncontaminated set of data. All results reported here are derived from the latter group. In subsequent analyses, we examined a subset of the study group sample for differences in age of onset of first psychiatric symptoms, course of illness and measures of symptom severity. These groups were compared using the chi-square procedure for categorical data and the Analysis of Variance (ANOVA) with Scheffe pair wise tests for continuous variables. The Child Bipolar Questionnaire V.2.0, the Yale–Brown Obsessive Compulsive Scale (YBOCS) and the Overt Aggression Scale (OAS) were the principal instruments used to obtain diagnostic information for this study.

To assess the relationship between membership in an FOH group and symptoms of mood dysregulation and psychiatric disorders, the CBQ was administered to all subjects ($N=1726$). The CBQ is a 65 item, self-administered, parent-report measure originally developed to establish initial eligibility for clinical and genetic studies of PBD (Papolos et al., 2006) It was constructed based on the model proposed by Depue et al. (1981), who, with the development and validation of the General Behavior Inventory (GBI), derived a dimensional approach for the definition of BPD in adults. Behaviors and symptoms are measured on 1–4 Likert scale. A rapid screening instrument with a Core Index subscale of key symptom dimensions frequently reported in PBD, the CBQ includes scoring algorithms for DSM-IV BD, with and without attention deficit/hyperactivity disorder (ADHD). Test/retest data showed excellent reliability for both the CBQ total score ($r=0.82$) and the Core Index subscale ($r=0.86$). CBQ screening algorithms were performed with a specificity of 97% and a sensitivity of 76% in classifying subjects with Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS P/L) diagnosis of BD vs. no BD (Papolos et al., 2006). The Core

Index subscale had excellent agreement with K-SADS P/L diagnosis (k = 0.84) in classifying BD, ADHD-only, and no diagnosis and demonstrated 100% sensitivity and 86% specificity in classifying BD vs. no BD. Consistent with a previous examination of the FOH symptom dimension (Papolos et al., 2005a), we used a YBOCS measure that consisted of a count of six aggressive obsessions rated by the parent as occurring at a frequency of "often" or "very often" or "almost constantly": [1] fear might harm self; [2] fear might harm others; [3] fear harm might come to self; [4] fear harm will come to others (may be because of something child did or did not do); [8] fear will act on unwanted impulses (e.g., to stab a family member); [10] fear will be responsible for something else terrible happening (e.g., fire, burglary, flood). The FOH index was calculated by summing six YBOCS items that had scored greater or equal to 3 and two items from OAS that had scored greater or equal to 2. The items from the OAS are: [11] mutilates self, causes deep cuts, bites that bleed internal injury, fracture, loss of consciousness, loss of teeth and [15] attacks others, causing severe physical injury.

Consistent with a previous examination of the FOH symptom dimension (Papolos et al., 2005a,b) YBOCS items that had scored greater or equal to 3 and two items from OAS that scored greater or equal to 2 defined the phenotype. A principal component factor analysis with Varimax rotation was used to determine what other traits are associated with the FOH trait by examining the independent factors derived from the CBQ. To determine the nature and extent to which each of these factors were associated with the FOH trait, a total score for each factor was calculated by summing all items for each factor and the factors were named based on item content. Cronbach's alpha was also calculated per factor. These factors were used in a multiple regression model to predict the Fear of Harm Index using a stepwise method. Some questions were not applicable to all subjects, resulting in different sample size per variable. The SPSS version 15 was used for all these analyses.

3. Results

Of the 2666 subjects, 1729 were found to have FOH data. When we examined the distribution of the FOH index in this sample, one of the most striking findings was that a full third of the group had no FOH ($X^2 = 169.14$, df = 1, $p < .001$). The total group of 1729 children was, therefore, divided into three groups. A group with no FOH symptoms (NoFOH), values of 0 positively endorsed items (NoFOH: 0 ± 0, $N = 621$, 36%), and subjects with values from 1 through 7 (LowFOH: 4.5 ± 2 $N = 555$, 32%) were designated as the low FOH group. The high FOH group included subjects with values greater than or equal to seven (HighFOH: 14.1 ± 5, $N = 553$, 32%).

Although there were no significant differences between rates of males and females on the Fear of Harm Index (female: 5.7 ± 6, male: 6.2 ± 7, $f = 2.1$, df = 1,1640, $p = .148$), there were significantly more male subjects in the LowFOH group (NoFOH: 35%, LowFOH: 45%, and HighFOH: 34%, $X^2 = 6.41$, df = 2, $p = .041$). There is no significant age difference among groups (NoFOH = 10.0 ± 4, $N = 585$; LowFOH = 10.2 ± 4, $N = 528$; HighFOH = 10.4 ± 4; $f = 1.7$; df = 2,1636; $p = .182$). However, there were significantly more ADHD subjects in the NoFOH group compared to HighFOH (NoFOH = 19%, LowFOH = 16%, HighFOH = 11%, $X^2 = 7.9$, df = 1, $p = .005$).

Despite the fact that the three groups did not differ on the number of subjects diagnosed with bipolar disorder (NoFOH = 83%, LowFOH = 86%, HighFOH = 86%, $X^2 = 1.13$, df = 2, $p = .57$), or major depressive disorder (NoFOH = 4%, LowFOH = 2%, HighFOH = 2%, $X^2 = 2.69$, df = 2, $p = .26$), using CBQ item scores we found that there was a significantly greater frequency of manic (NoFOH = 5.0 ± 2, LowFOH = 5.7 ± 1, HighFOH = 5.6 ± 2; $f = 79.43$; df = 2,1726; $p < .0001$) and depressive symptoms (NoFOH = 3.9 ± 2, LowFOH = 4.6 ± 2, HighFOH = 4.9 ± 2; $f = 60.53$; df = 2,1726; $p < .0001$) in the high FOH group when compared to the low or no FOH groups. Pair wise tests indicate that all groups are significantly different from each other on these variables. These differences are also evident when the dimensions were dichotomized (Table 1). The HighFOH group has a significantly greater number of subjects with five or more manic/hypomanic symptoms, 91%, compared to the LowFOH group of 83% and NoFOH group of 69% of subjects ($X^2 = 93.8$, df = 2, $p < .000$). All pair wise comparisons were also significant. The differences persisted when analyzed for depressive symptoms; 84% of the HighFOH group exhibited four or more symptoms of depression in comparison to 78% of the LowFOH and 62% of NoFOH groups ($X^2 = 76.4$, df = 2, $p < .0001$). All pair wise comparisons were also significant. Similar results were found when groups were compared separately for male and female subjects (Table 1).

Course of illness data was available for 967 children. Within this subgroup we applied the same criteria for FOH status. Similar to the larger pool of children, this smaller group contained about a third of children who endorsed 0 items of FOH ($N = 334$, 35%), a third endorsed 1 through 7 items ($N = 322$, 33%) and a third endorsed more than 7 items ($N = 311$, 32%). The similarity of the distribution of FOH in each group raises one's confidence that this smaller subset of children is a representative sample of the larger sample.

The three groups endorsed CBQ items significantly differently from each other ($f = 137.69$; df = 2,981; $p < .001$). The NoFOH group positively endorsed 37.9 ± 11 items, LowFOH 45.8 ± 8 items and the HighFOH group positively endorsed 49.6 ± 8 items. These differences were similar to the larger group. The groups were not significantly different in age (NoFOH = 9.7 ± 4, LowFOH = 9.9 ± 4, HighFOH = 10.3 ± 4; $f = 2.10$; df = 2,896; $p = .122$). The groups had a similar distribution of male subjects (NoFOH: 33%, LowFOH: 30%, and HighFOH: 36%, $X^2 = 5.11$, df = 2, $p = .077$).

These groups had a similar age of onset of first reported psychiatric symptoms, age of initial psychiatric evaluation, age of initial diagnosis and age at first psychiatric hospitalization. However, they were significantly different on the number of hospitalizations (Table 2). The NoFOH group has

Table 1
Group differences on symptoms of mania and depression mania and depression symptoms ($N = 1729$).

	NoFOH	LowFOH	HighFOH	X^2 *
Manic symptoms greater or equal to 5	69% (426)	83% (459)	91% (502)	93.8
Depressive symptoms greater or equal to 4	62% (387)	78% (431)	84% (464)	76.4

* $p < .001$.

Table 2
Course of illness ($N=967$).

	NoFOH	LowFOH	HighFOH	f	$p<.01$
Age of 1st symptoms (years)	2.7±2 ($N=334$)	2.6±3 ($N=322$)	2.5±2 ($N=311$)	1.12	.326
Age of initial psychiatric evaluation (years)	6.0±3 ($N=316$)	6.0±3 ($N=312$)	6.0±3 ($N=300$)	.037	.963
Age of initial diagnosis (years)	6.3±3 ($N=306$)	6.5±5 ($N=313$)	6.3±4 ($N=302$)	.365	.694
Age of 1st psychiatric hospitalization (years)	9.7±4 ($N=78$)	9.6±4 ($N=114$)	9.4±4 ($N=164$)	.337	.713
Number of hospitalizations	1.5±1 ($N=86$)	1.8±2 ($N=118$)	2.4±2 ($N=172$)	6.31	.002 *

* Significant pair wise comparisons based on Scheffe formula: NoFOH vs. LowFOH ($p=.005$) and vs. HighFOH ($p=.044$).

a significantly fewer number of hospitalization than the other two groups.

On measures of severity of illness presented in Table 3, there were significant differences found among the FOH groups on the severity of illness variables; Ever Hospitalized, Held Back a Grade, and Suspended from School. However, the groups were not significantly different on home schooling and their involvement with the juvenile justice system. All groups were significantly different from each other on ever hospitalized with HighFOH has the largest percentage of subjects (52%). Significantly more subjects from the HighFOH group were also held back a grade compared to NoFOH ($X^2=8.49$, df=1, $p=.004$) and significantly more subjects from HighFOH and LowFOH were suspended from school than NoFOH ($X^2=8.48$, df=1, $p=.004$; $X^2=6.24$, df=1, $p=.012$). There was a strong trend between held back a grade and suspended from school. 47% of subjects who were held back a grade were also suspended from school ($X^2=2.75$, df=1, $p=.098$). 14% of subjects from HighFOH groups were suspended from school and held back a grade compared to 7% from NoFOH ($X^2=7.39$, df=1, $p=.007$) and 6% subjects from LowFOH groups ($X^2=11.30$, df=1, $p=.001$).

Using all of the children in the study, a principal component factor analysis was used to identify a set of independent dimensions associated with the FOH trait of children ($N=1729$; NoFOH=621, LowFOH=555, HighFOH=553). The factor analysis yielded thirteen factors with eigenvalues greater than 1.0 that explained a total of 61% of variance. By combining 3 of the factors with the lowest Cronbach's alpha with other factors to which they also contributed, we reduced the 13 factors to 10. These ten factors their CBQ items, eigenvalues, percentage of variance and the Cronbach's alphas are listed in Table 4.

Descriptive information for each CBQ factor for the three FOH groups are presented in Table 5.

The mean number of CBQ items endorsed by the three FOH groups was significantly different from each other. The NoFOH group positively endorsed 37.9±11 items (out of 65 items), LowFOH 45.05±9 items and the HighFOH group positively endorsed 49.99±8 items ($f=243.27$; df=2,1726; $p<.001$). Subjects who scored either HighFOH or LowFOH were found to have more severe symptoms on all of these CBQ factors than children without the FOH trait.

We sought to determine what other traits are associated with the FOH trait by examining the 10 independent factors derived from the CBQ using a multiple regression analysis. The regression analysis resulted in a six factor model being the best fit. The 6 factors that emerged accounted for 45% of the variance (Step 6: F=148.65; df=6,1076; p=.000). These factors are: Territorial Aggression, Harm to Self and Others, Self-esteem, Psychosis/Parasomnias/Sweet Craving/Obsessions (PPSO), Sleep, and Anxiety.

4. Discussion

In this study we sought to further elucidate a dimensional behavioral phenotype of PBD. This phenotype was originally defined in a concordance study of affected sibling pairs that examined the heritability of CBQ factors in a group of subjects with a community diagnosis of PBD (Papolos et al., 2007). Six of these factors, including a Core Index of 22 CBQ items, exhibited the strongest concordance coefficients between probands and siblings and the widest contrasts between proband/sibling vs. proband/comparison pairs. These factors were: Fear of harm, Aggression, Anxiety, Sensory sensitivity, Sleep/wake cycle disturbances, and Attention/Executive function deficits. This suggested to us a profile of heritable clusters of CBQ symptoms, that, in addition to classic mood symptoms, could provide distinguishing features of novel phenotypes of PBD (Papolos et al., 2007). We hypothesized that in addition to mania and depression, heritable trait features such as FOH could be instrumental in elucidating a specific behavioral phenotype derived from a factor analysis of CBQ symptom dimensions. Indeed, we found that subjects with FOH had significantly higher frequencies of both manic and depressive symptoms than the no or low FOH groups, suggesting that the subjects who carry this trait feature fall clearly within the domain of classical manic-depression, and that the presence and severity of FOH symptoms is a defining feature of this phenotype (Kraepelin, 1976; Goodwin and Jamison, 2007).

It has been suggested that an earlier age of onset may further separate patients with BD into more homogeneous

Table 3
Group differences on measures of severity of illness.

	Yes	NoFOH (%)	LowFOH (%)	HighFOH (%)	X^2	p value
Ever hospitalized ($N=984$)	352	22	34	52	63.7	.001
Home schooled ($N=984$)	40	5.4	4.3	2.2	4.7	.094
Held back a grade ($N=880$)	171	15	20	24	8.5	.014
Ever suspended from school ($N=905$)	366	36	38	48	9.9	.007
Involved with the juvenile justice system ($N=984$)	110	91	89	86	5.1	.079

Table 4

Factor	CBQ items	Eigenvalues	% Variance	α
Factor 1: Territorial Aggression	46) is willful and refuses to be subordinated by others	16.56	25.5	.91
	47) argues with adults			
	49) defies or refuses to comply with rules			
	51) is easily angered in response to limit setting			
	48) is bossy towards others			
	45) relentlessly pursues own needs and is demanding of others			
	50) blames others for his/her mistakes			
	53) has protracted, explosive temper tantrums			
	55) displays aggressive behavior towards others			
	32) has irritable mood states			
	52) lies to avoid consequences of his/her actions			
	44) is intolerant of delays			
	54) has difficulty maintaining friendships			
Factor 2: Attention/Executive function	17) has difficulty organizing tasks	3.71	5.7	.87
	13) demonstrates inability to concentrate at school			
	12) is easily distracted during repetitive chores and lessons			
	14) attempts to avoid homework assignments			
	16) has poor handwriting			
	11) is easily distracted by extraneous stimuli			
	19) has difficulty estimating time			
	15) able to focus intently on subjects of interest and yet at times is easily distractible			
	20) has auditory processing or short-term memory deficit			
	18) has difficulty making transitions			
Factor 3: Mania	25) has periods of high, frenetic energy and motor activation	3.24	4.9	.87
	28) has periods of excessive and rapid speech			
	26) has many ideas at once			
	33) has elated or silly, goofy, giddy mood states			
	24) is easily excitable			
	27) interrupts or intrudes on others			
	04) is hyperactive and easily excited in the PM			
	31) displays abrupt, rapid mood swings			
	43) fidgets with hands or feet			
	65) is very intuitive and/or very creative			
	30) tells tall tales; embellishes or exaggerates			
	29) has exaggerated ideas about self or abilities			
Factor 4: Harm to Self/Others	59) makes clear threats of violence to others or self	2.93		.83
	58) makes moderate threats to others or self			
	60) has made clear threats of suicide			
	57) curses viciously, uses foul language in anger			
	56) has destroyed property intentionally			
	61) is fascinated with gore, blood, or violent imagery			
Factor 5: Self-esteem	41) feels easily criticized and/or rejected	2.40		.84
	42) feels easily humiliated or shamed			
	40) experiences periods of self doubt and poor self-esteem			
	37) complains of being bored			
	38) has periods of low energy and/or withdraws or isolates self			
	39) has decreased initiative			
Factor 6: Sleep	06) has difficulty getting to sleep	1.93		.74
	05) has difficulty settling at night			
	07) sleeps fitfully and/or awakens in the middle of the night			
	03) has difficulty arising in the AM			
Factor 7: Sensory	21) is extremely sensitive to textures of clothes, labels, and tightness of fit of socks or shoes	1.78		.71
	22) exhibits extreme sensitivity to sound and noise			
	23) complains of body temperature extremes or feeling hot despite neutral ambient temperature			
Factor 8: Hypersexuality	34) displays precocious sexual curiosity	1.50		.74
	35) exhibits inappropriate sexual behaviors, e.g. openly touches self or others' private parts			
	36) takes excessive risks			
Factor 9: Psychosis, Parasomnias, Sweet Cravings, and Obsessions	09) wets bed	1.23		.59
	08) has night terrors and/or nightmares			
	63) hoards or avidly seeks to collect objects or food			
	62) has acknowledged experiencing auditory and/or			

(continued on next page)

Table 4 (*continued*)

Factor	CBQ items	Eigenvalues	% Variance	α
	visual hallucinations			
	10) craves sweet-tasting foods			
	64) has concern with dirt, germs, or contamination			
Factor 10: Anxiety	01) displays excessive distress when separated from family	1.03		.66
	02) exhibits excessive anxiety or worry			

α: Cronbach's alpha.

phenotypic subgroups for genetic studies (Todd et al., 1993; Leboyer et al., 1998; Bellivier, 2003; Papolos, 2003; Faraone et al., 2004; Leboyer et al., 2005; Engstrom et al., 2003). While the low and high FOH groups did not differ from the NoFOH group on age of first psychiatric symptoms and diagnosis, nor on age at first psychiatric hospitalization they had a significantly greater number of hospitalizations. The median ages for all three groups on first onset of symptoms for the first psychiatric diagnosis (NoFOH 2.7±2 LowFOH 2.6±3, and High FOH 2.5±2), or first psychiatric hospitalization respectively (NoFOH 9.7±4, LowFOH 9.6±4, and HighFOH 9.4±4) was surprisingly young. We also examined the difference between groups on course of illness variables. On measures of school performance, subjects positive for FOH were significantly more likely to be held back a grade and to be suspended from school. Taken together these findings suggest that all groups are of significant clinical importance. These children have severe psychiatric illness and impairment, very early age of onset, are highly socially impaired, and may have learning deficits. There was a greater incidence of comorbid ADHD in children without the FOH trait. The FOH group therefore, may represent a more homogeneous and perhaps more severe phenotype given the higher rates of hospitalization, and greater likelihood of school performance difficulties. In an extensive review of clinical, epidemiological, neurobiological, and genetic studies in bipolar disorder, Hasler et al. (2006) concluded that particular symptom dimensions, deficits, and physiological anomalies deserve further research focus as candidate endophenotypes that could improve the phenotypic definition of bipolar disorder. Such an approach has proved fruitful in the study of obsessive–compulsive (OCD) symptoms. By stepping outside the traditional DSM-IV diagnostic boundaries and applying findings from factor-analytic studies that consistently identified four temporally stable symptom dimensions: contamination/washing, aggressive/checking, hoarding, and symmetry/ordering (1–7), and examining these OCD symptom dimensions independently, Mataix-Cols et al. (2004, 2005, 2007, 2008) determined that a different activation pattern on fMRI is associated with each symptom dimension of OCD. Furthermore, they found that different dimensions are mediated by relatively distinct components of frontostriatothalamic circuits. They concluded that OCD may be best conceptualized as a spectrum of multiple, potentially overlapping syndromes rather than a unitary nosologic entity. Similarly, we utilized a factor-analytic approach of symptom dimensions of PBD derived from the CBQ that we believe provides further support for this method as a means to dissect phenotypes of complex psychiatric disorders. As currently defined, PBD is a clinically heterogeneous condition. This heterogeneity can reduce the power and obscure the findings from natural history studies to genome scans, neuroimaging, and clinical trials. It has been suggested that when the boundaries of a syndrome are in question, as in the case with PBD, dimensional analysis may yield more information about the specific symptoms or constellations of symptoms that define a syndrome (Kendell and Jablensky, 2003). We believe this approach finds further support from this study and underscores the farsightedness of Mataix-Cols and colleagues for pointing the field in this direction. By examining other dimensional features of the FOH trait in enriched samples of large size we were able to further refine what appears to be a subphenotype of pediatric bipolar disorder. The complex clinical presentation of PBD can be understood as a spectrum of potentially overlapping syndromes that may 1) coexist in any patient, 2) be continuous with classical manic and depressive symptoms and 3) extend beyond the traditional nosological boundaries of BPD that tend to obscure symptoms not central to the construct of a particular disorder.

The FOH phenotype is a clinically homogeneous behavioral phenotype of PBD with early age of onset, severe manic and depressive symptoms, early and frequent psychiatric hospitalizations, significant social impairment and school problems that can be identified using 6 factors derived from the CBQ with 96% accuracy. Given the potential for early intervention in such a group of very severely ill children that engender an enormous psychic, social, and financial burden to parents, teachers, medical and social agencies that have responsibility for their care, the CBQ is being widely used as an early screening tool by child psychiatrists, child psychologists, social workers, and pediatricians (The Juvenile Bipolar Research Foundation (http://www.bpchildresearch.org/cpp/index.html)). Although the dimensional structure of symptoms derived from the CBQ to define a subtype of PBD is imperfect, this quantitative approach to the identification of phenotypic traits has the potential to advance our

Table 5
Bipolar Child Questionnaire Factor Scores: Mean Standard Deviations Across FOH Groups.

	NoFOH	LowFOH	HighFOH	Factor group mean
Territorial Aggression [a]	39.8±9	43.5±7	46.5±5	43.1±8
Attention/Executive function	30.9±7	33.1±5	34.5±5	32.8±6
Mania	36.1±7	39.0±6	41.3±5	38.7±7
Harm to Self/Others [a]	11.9±4	14.5±4	17.6±4	14.5±5
Self-esteem [a]	17.3±4	18.9±4	20.1±4	18.7±4
Sleep [a]	11.5±3	12.5±3	13.0±3	12.3±3
Sensory	7.4±3	8.1±3	8.8±3	8.1±3
Hypersexuality	5.7±2	6.5±3	7.3±3	6.5±3
Psychosis/Parasomnias/Sweet Cravings/Obsessions [a]	11.5±3	13.2±3	14.6±4	13.0±4
Anxiety [a]	4.7±2	5.5±2	5.9±2	5.3±2

[a] These are the significant factors that emerged with multiple regression analysis of the factor structure.

understanding of PBD and may prove fruitful in both differential diagnosis and etiological studies. The specificity of the CBQ factor items that define the FOH subtype including, Territorial Aggression, Harm to Self and Others, Self-esteem, and Psychosis/Parasomnias/Sweet Craving/Obsessions (PPSO) has lead us to propose a hypothesis that predicts the biological underpinnings of the endophenotype.

The PPSO factor comprises a unique cluster of symptoms that includes psychosis, parasomnias (enuresis and night terrors), craving for sweets, food hoarding and contamination fears, and suggests the phenotype is characterized by disturbances in appetite, as well as sleep/arousal systems. In juvenile bipolar disorder, disturbances in the quality of both sleep and wakefulness are prominent. Preliminary data from parental reports of children with PBD indicate that a diverse set of sleep problems particularly sleep-onset delay and sleep fragmentation and morning sleep inertia are severe and more frequent relative to children with other psychiatric disorders, primary sleep disorders, in a community sample of children. (Harvey et al., 2006; Mehl et al., 2006a,b; Murphy et al., in press).

Preliminary data from temperature/actigraphy studies of pediatric bipolar disorder suggest that one of the features of the condition is a delay of circadian sleep and temperature rhythms that would produce symptoms of initial insomnia and sleep inertia (sleep onset and sleep offset) (unpublished data). Also, pilot data from children with the FOH phenotype suggest that there is a circadian phase delay in sleep timing and temperature dysregulation at sleep onset. Difficulty arising in the AM (sleep inertia), settling at night, getting to sleep and sleeping fitfully or awakening in the middle of the night constitute sleep initiation and maintenance problems that specifically characterize the FOH Sleep/Arousal factor. In addition, arousal parasomnias, including enuresis, hypnogogic and hypnopompic hallucinations, night terrors and vivid nightmares — often containing images of gore and mutilation, themes of pursuit, bodily threat and parental abandonment are features of the PPSO factor. Taken together this set of symptoms is indicative of both primary sleep problems and sleep pertubations secondary to altered circadian and ultradian rhythms of sleep, wakefulness and temperature (Lack et al., 2008; Poceta et al., 2009; Pal and Mallick, 2007). Disturbances in areas that regulate these rhythms would likely result in difficulties with transitions from sleep to waking, waking to sleep and between REM and NREM sleep phases.

Cumulative evidence indicates that hypothalamic preoptic area orexigenic neurons are active during sleep and in response to the increase in homeostatic pressure for sleep. They orchestrate onset, offset and maintenance of sleep as well as the regulation of REM/nonNREM sleep transitions by inhibitory modulation of multiple arousal systems (de Lecea et al., 1998; Willie et al., 2001; Fujiki et al., 2009; Mieda et al., 2004; Yamanaka et al., 2003; Oldfield et al., 2007; Hirota, 2007; Szymusiak and McGinty, 2008; Galvão et al., 2009). Regulation of vigilance states by orexin neurons operates through two orexin receptor subtypes. Noradrenergic neurons in the locus coeruleus express orexin A, and histaminergic neurons in the tuberomammillary neurons (TMN) express orexin B, while serotonergic neurons in the dorsal raphe express both receptor subtypes. Orexin neurons in the lateral hypothalamic nucleus send excitatory projections to monoaminergic neurons. Studies in knockout mice suggest that activation of (TMN) histaminergic neurons via orexin B is crucial for maintenance of arousal and gating of non-REM sleep, while both receptors may prevent entry into REM sleep (de Lecea et al., 1998; Hagan et al., 1999; Ohno and Sakurai, 2008).

Disruption of the orexin system results in human narcolepsy, characterized by excessive daytime sleepiness, premature transitions to REM sleep (sleep-onset REM), and cataplexy (Mieda et al., 2004; Fujiki et al., 2009; Mishima et al., 2008; Douglass, 2003). A transgenic method that mapped upstream neuronal populations with synaptic connections to orexin neurons revealed that these neurons receive input from several brain areas, including the amygdala, basal forebrain cholinergic neurons, GABAergic neurons in the preoptic area, and serotonergic neurons in the median/paramedian raphe nuclei (Ohno and Sakurai, 2008). Produced in a very sparse population of cells in the lateral and posterior hypothalamus, orexin neurons send widespread projections throughout the brain and heavily innervate many wake-promoting regions such as the locus coeruleus as well as those regions involved in food-seeking behaviors and the ventral tegmental area (VTA), the origin of dopamine projections implicated in motivation and reward (Peyron et al., 1998; de Lecea et al., 1998; Marcus et al., 2001; Sutcliffe and de Lecea, 2000; Mochizuki et al., 2006). In addition, orexin neurons project densely to the preoptic area which is involved in thermoregulation (Parmeggiani et al., 1986; Boulant, 2000; Yoshimichi et al., 2001; Capitani et al., 2005; Burdakov and González, 2008; Morrison et al., 2008). An emerging body of evidence from both adults and children support the notion that thermoregulatory processes are critical in the regulation of sleep. Specifically, the ability to dissipate heat efficiently at night is permissive of sleep onset, and the capacity to conserve heat efficiently in the morning reduces sleep inertia and promotes wakefulness. The PPSO and Sleep/Arousal symptoms can be viewed as a reflection of dysregulation of homeostatic functions that are closely associated with the rise and fall of body temperatures — the relationship between these thermoregulatory variables at the appropriate time of day promote sleep onset and sleep offset and potentially the timing function that alternates between NREM and REM sleep phases.

Sweet craving and food hoarding are primary symptoms of the PPSO FOH factor. Orexin A and NPY-induced orexigenic actions modulate behavioral state and state-dependent processes. Evidence suggests that the mechanism of orexin action is directly related to synaptic regulation of the NPY system (Horvath et al., 1999; Tavas et al., 1999; Kalra et al., 1999; Yamanaka et al., 2000; Kalra and Kalra, 2004; Glavas et al., 2008). NPY is the most robust physiological appetite transducer known (Day et al., 2009). Orexin A also induces acute feeding (Preti, 2002). The circadian and ultradian rhythmicities in NPY secretion imprint the daily circadian and episodic feeding patterns. NPY is a potent peptide that increases food foraging and hoarding (appetitive behavior) and food intake (consummatory behavior) (Williams et al., 2001; Jain et al., 2000; Yoshida et al., 2001; Kalra and Kalra, 2004; Day et al., 2005; Keen-Rhinehart and Bartness, 2007; Olszewski et al., 2009; Day et al., 2009).

The CBQ factors, Territorial Aggression and Harm to Self and Others are two other significant traits that define the FOH phenotype. These two factors comprised of symptoms that

reflect high levels of aggression and fear as well as defensive or reactive aggressive behaviors. Karl et al. (2004) established a relationship between territorial aggression and feeding behavior in animals through the identification of a neural circuit by which the NPY Y1 receptors may affect both behaviors. Fear arousal, initiated by a perceived threat, leads to activation of the stress response, a state of alarm that promotes an array of cortico-limbic, autonomic pathways and endocrine changes associated with fight or flight behaviors designed to aid self-preservation (Zhou et al., 2008; Rodrigues et al., 2009). NPY release is induced by stress, decreases fear-related behaviors in various animal models of anxiety and is abundantly expressed in regions of the limbic system that are implicated in arousal and in the assignment of emotional valences to fear stimuli and memories (long term potentiation) (Jiménez-Vasquez et al., 2001; Sørensen et al., 2008, 2009; Gutman et al., 2008). NPY dampens the excitability of amygdaloid neurons and inhibits both baseline acoustic startle and the expression of fear-potentiated startle behaviors, and is anticonvulsant (Sosulina et al., 2008; Rodrigues et al., 2009). This neuropeptide circuit is clearly involved in territorial aggressive behaviors, fear sensitization, foraging and hoarding behaviors in animals.

In sum, we suggest that a complex orexigenic neuropeptide circuit first delineated by Emeson and Morabito (2005), that links the hypothalamic nuclei, the median preoptic nucleus (MnPO), ventrolateral preoptic nucleus (VLPO), and the suprachiasmatic nucleus (SCN), as well as the olfactory bulb, amygdala, ventral tegmental nucleus, nucleus accumbens, median and dorsal raphe nuclei, and the locus coeruleus, is primarily responsible for the regulation of the behavioral and proposed physiological features of the FOH phenotype.

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Conflict of interest

Dr. Papolos developed the Child Bipolar Questionnaire which was the primary instrument used in this research. He derives minimal financial benefit from the use of the questionnaire by clinicians. The survey is also used in research free of charge.

Dr. Golshan reports no financial or personal conflicts of interest that could inappropriately influence, or be perceived to influence the work reported here.

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Research paper

Obsessive fears about harm to self or others and overt aggressive behaviors in youth diagnosed with juvenile-onset bipolar disorder

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Abstract

Background: Obsessive fear-of-harm, either fear of doing harm or fear of harm coming to self, may be closely associated with aggressive behaviors in juvenile-onset bipolar disorder.
Methods: We analyzed parent-report data on the Yale–Brown Obsessive Compulsive Scale (YBOCS) and Overt Aggression Scale (OAS) for 1601 children/adolescents with a clinician-assigned diagnosis of bipolar disorder. The summing of 6 YBOCS items rated "often" or "very often or almost constant" yielded a biphasic distribution of scores. Median-split was used to define meaningful subgroups contrasting high vs. low "fear-of-harm", which were then compared on parent-reported severe injury to self and others and on parent-reported suicide threats.
Results: High fear-of-harm was strongly associated with parent-reported severe injury to self and others. For self-injury, the estimated risk ratio for high vs. low fear-of-harm subgroups was 2.68 (95% confidence interval 1.87–3.86), indicating greater than doubling of risk associated with high fear-of-harm. For severe injury to others, the estimated risk ratio was 7.97 (95% confidence interval 4.19–15.2), suggesting a nearly eight-fold increased risk associated with high fear-of-harm. High fear-of-harm subjects were reported to make serious suicide threats much more frequently than low fear-of-harm subjects (odds ratio, estimated by ordinal logistic regression modeling methods, was 2.42 (95% CI 2.00 to 2.92; $z=9.12$, $p<0.001$).
Limitations: Child report data was not obtained; clinician diagnosis was not validated via research interview.

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Conclusions: Obsessive fears about harm to self or others in a sample of children with a clinician-assigned diagnosis of bipolar disorder were found to be positively related to increased behavioral aggression towards self and others, as well as to frequent suicide threats.

Keywords: Obsessive fears; Fear-of-harm; Bipolar disorder; Juvenile-onset bipolar disorder; Aggression; Self-harm

1. Introduction

Obsessive fear about harm to self or others is observed in several childhood psychiatric conditions, including obsessive–compulsive disorder, separation anxiety disorder, and bipolar disorder. For some young patients, fear of harm may reflect a low threshold for anxiety, or it may be associated with hallucinatory or delusional images. Some evidence suggests that in bipolar patients, fear of harm may result from misattribution of threat to neutral social cues. Bipolar adults have demonstrated impaired recognition of facial emotion (Lembke and Ketter, 2002), and bipolar youth have demonstrated a bias to misidentify faces as angry (McClure et al., 2003).

Clinical experience with bipolar youth suggests that those most anxious about harm coming to themselves or others are also physically and verbally aggressive. The current debate about the cardinal features of juvenile mania and its differentiation from other psychiatric disorders has placed strong emphasis on the relationship of anxiety and paranoia to aggressive behavior. A recently published report notes, "it is important that particular care be given to assessing anxiety and subtle forms of paranoia in children with irritable (hypo)mania or mixed episodes, especially those who exhibit aggressive behavior" (Leibenluft et al., 2003a,b). Others who have investigated the features of anxiety and aggression in childhood bipolar disorder concur (Dilsaver and Chen, 2003; Masi et al., 2004; Post et al., 2004).

In this study, we inquired whether bipolar children and adolescents with recurrent fears of harm were more behaviorally aggressive than those with fewer, less obsessive fears. Using an extensive, Internet-based data acquisition system established by the Juvenile Bipolar Research Foundation (JBRF, 2004), we obtained data on obsessive fears via parents' responses on the Yale–Brown Obsessive Compulsive Scale [YBOCS] (Goodman et al., 1989), and on aggressive behaviors via parents' responses on the Overt Aggression Scale [OAS] (Yudofsky et al., 1986). In this report, we summarize data on the relationship between parent-reported fear of harm and parent-reported aggressive behavior in children assigned a formal diagnosis of bipolar disorder by a clinician.

2. Methods

2.1. Data acquisition

The JBRF has established an extensive, Internet-based system for data acquisition on children clinically diagnosed with bipolar disorder (JBRF, 2004). Sample selection for this study was based on parent report that the child/adolescent had been diagnosed with bipolar disorder by a clinician in the community. All subjects were assessed using the YBOCS, the OAS, and the Child Bipolar Questionnaire [CBQ] (Papolos and Papolos, 2002), a 65-item Likert-scale instrument used to screen for juvenile-onset bipolar disorder.

2.2. Fear-of-harm index

A fear-of-harm index was calculated by summing 6 YBOCS items occurring at a frequency of "3" ("often") or "4" ("very often or almost constantly"): [1] Fear might harm self; [2] Fear might harm others; [3] Fear harm might come to self; [4] Fear harm will come to others (may be because of something child did or did not do); [8] Fear will act on unwanted impulses (e.g., to stab a family member); [10] Fear will be responsible for something else terrible happening (e.g., fire, burglary, flood). The distribution of scores on this measure was distinctly biphasic. We used med-

ian-split to define meaningful subgroups contrasting high vs. low fear-of-harm. These two subgroups were compared on OAS subscales and OAS total score, as well as on the two most severe OAS items: [11] Mutilates self, causes deep cuts, bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth; [15] Attacks others, causing severe physical injury (broken bones, deep lacerations, internal injury).

In addition, in order to assess possible connections between fear-of-harm and suicidality, we compared high and low fear-of-harm subjects on a CBQ item assessing suicide threats: [60] Has made clear threats of suicide. Parent-reported suicide threats rated "very often or almost constantly" were coded as present and those rated "never or hardly ever," "sometimes," or "often" were coded as not present.

2.3. Statistical methods

We contrasted rates of high fear-of-harm between males and females and correlated this measure with each of several count or continuous measures characterizing the study sample, including the number of psychotropic medicines, the number of psychiatric diagnoses reported, and the OAS total score, using generalized linear modeling methods with binomial family and logarithmic link, to obtain a risk ratio (RR) and its 95% confidence interval (95% CI) for each of these explanatory factors. We contrasted children identified by parents on the Overt Aggression Scale as having frequent episodes of (A) self-harm, or (B) attacks on other persons, on three dimensions: males vs. females, older children (age >10) vs. younger, and fear-of-harm high vs. not-high. In these contrasts, risk ratios and their 95% CIs were obtained, using generalized linear modeling methods. We contrasted parental report of frequency of suicidal threats (CBQ Item 60) between high vs. low fear-of-harm subgroups, using $\chi^2[df=3]$ methods, and we obtained an adjusted odds ratio assessing the strength of the association between frequency of suicidal threats and high vs. low fear-of-harm indicator using ordinal logistic regression modeling methods. Model fits were checked using graphical methods. Robust standard error estimates were made when feasible. Averaged continuous data are reported as means with standard deviations ($\pm$SD) or 95% CIs. Statistical significance required 2-tailed $p<0.05$. Analyses employed commercial microcomputer programs (Stata®, Stata Corp., College Station, TX).

3. Results

There were 2262 subjects for whom both YBOCS and OAS data were obtained via the JBRF Internet-based system. 1601 (70.8%) of these children had been formally assigned a diagnosis of bipolar disorder by a clinician (i.e., child psychiatrist, psychiatrist, pediatrician, or other clinician), according to their parents. They comprised the study group for this report. 617 (37.3%) scored in the high fear-of-harm subgroup and 1039 (62.7%) scored in the low fear-of-harm subgroup. 425 (68.9%) of the high fear-of-harm subgroup were male vs. 629 (60.5%) of the low fear-of-harm subgroup, ($p=.001$). The average age of the high fear-of-harm subgroup was 10.6 years $\pm$ 3.3 (2–18) vs. 11.4 years $\pm$ 3.7 (2–20) for the low fear-of-harm subgroup, ($p<.001$). The average number of psychotropic medicines prescribed to the high fear-of-harm subgroup was 2.41 $\pm$ 1.6 (0–18, $n=327$); the average number prescribed to the low fear-of-harm subgroup was 2.21 $\pm$ 1.4 (0–10, $n=576$), ($p=.060$). The average number of psychiatric diagnoses given to the high fear-of-harm subgroup was 3.35 $\pm$ 2.1 (0–9, $n=327$); the average number given to the low fear-of-harm subgroup was 2.75 $\pm$ 1.8 (0–9, $n=576$), ($p<.001$).

3.1. OAS and YBOCS measures

There was a very large difference between the two fear-of-harm subgroups on average OAS total score (11.8 $\pm$ 3.5 vs. 8.80 $\pm$ 4.8), with a difference at the mean of more than 34%. Summary data on the most severe OAS item measures of harms-self (Item 11) and harms-others (Item 15) are provided in Table 1. These data indicate that children/adolescents identified as having high fear-of-harm anxieties were 2.7-fold (RR = 2.68) more likely to be identified by their parents as engaging in severely self-injurious behaviors than subjects with relatively low fear-of-harm anxieties; and these same children were 8-fold (RR = 7.97.4) more likely to be identified as engaging in severely injurious assaults on others. Older children were more likely to be identified by their parents/guardians as engaging in

Table 1
Characteristics of children reported by parents as Yes and No on Overt Aggression Scale items indicating severe symptoms of (A) self-harm or (B) attacks on other persons

Measure[a]	Yes on OAS item	No on OAS item	Risk[b] ratio	(95% CI)[b]	z	p
A. OAS Item 11 (self-harm)[c]						
Number (%)	114 (7.1)	1487 (92.9)	–	–	–	–
Males	66/114 (57.9)	950/1487 (63.9)	0.79	0.55–1.13	−1.28	0.20
Age>10 years	79/114 (69.3)	863/1477 (58.4)	1.56	1.06–2.29	2.25	0.025
Fear-of-harm>median	70/114 (61.4)	526/1487 (35.4)	2.68	1.87–3.86	5.32	<0.001
B. OAS Item 15 (harm to others)[d]						
Number (%)	63 (3.9)	1538 (96.1)	–	–	–	–
Males	45/63 (71.4)	971/1538 (63.1)	1.44	0.84–2.46	1.33	0.18
Age>10 years	29/63 (46.0)	913/1528 (59.8)	0.59	0.36–0.95	−2.15	0.032
Fear-of-harm>median	52/63 (82.5)	544/1538 (35.4)	7.97	4.19–15.2	6.33	<0.001

[a] Fear-of-harm high vs. low subgroups defined by median-split on 6 YBOCS "fear-of-harm" items, together with YBOCS frequency ratings of at least 2 (often) on each of these 6 items.
[b] Risk ratio and 95% CI estimated using generalized linear modeling (GLM) methods.
[c] OAS Item 11: Mutilates self, causes deep cuts/bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth. Current behavior rated Yes/No by parents/guardians.
[d] OAS Item 15: Attacks others, causing severe physical injury (broken bones, deep lacerations, internal injury) mutilates self, causes deep cuts/bites that bleed, internal injury, fracture, loss of consciousness; rated Yes/No.

very severe self-harm behaviors, but younger children were more likely to be identified as engaging in severe harm-to-others behaviors.

The six YBOCS fear-of-harm items very strongly separate children and adolescents who were/were not identified by their parents/guardians as actively engaging in severe harm-to-others behaviors. This is illustrated graphically in Fig. 1, which shows the count of the number of YBOCS fear-of-harm items endorsed by parents in relation to whether the child

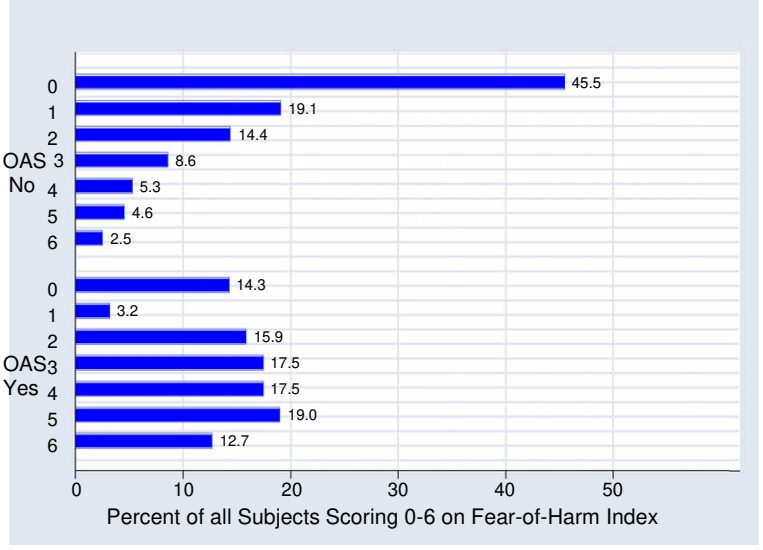

Fig. 1. Bar graph showing fear-of-harm index scores based on six YBOCS items for two subgroups: subjects scored as Yes vs. No on the Overt Aggression Scale "severe attacks on others" item. YBOCS-based fear-of-harm index is a count (0/6) of the number of items scored at a frequency of 3 ("very often or almost constantly") or higher.

was/was not identified as exhibiting severe harm-to-others behaviors on OAS Item 15. The figure shows a very clear separation between subjects with/without overt harm-to-others behavioral patterns. In a small ($N=81$) healthy comparison group, these fear-of-harm–overt aggressive behavior correlations were near-zero.

3.2. Fear-of-harm and suicidality

YBOCS and CBQ data were available for 1696 subjects. Parents of the high fear-of-harm children/adolescents ($N=617$, 37.3%) were much more likely to report that their children frequently threatened suicide on CBQ Item 60 ("Has made clear threats of suicide") than parents of the remaining subjects ($N=1039$). Fully one-quarter (27.2%) of the parents of the high fear-of-harm subjects indicated that their sons/daughters made clear threats of suicide with frequency "very often or almost constantly." This percentage was more than twice the corresponding percentage among all other parents providing both YBOCS data and suicide threat (CBQ Item 60) data. When examined using ordered logistic regression modeling methods, the estimated odds ratio was 2.42 (95% CI 2.00 to 2.92; $z=9.12$, $p<0.001$).

4. Discussion

In this study, we examined the hypothesis that recurrent, intense fears about harm to self or others in a sample of children diagnosed with bipolar disorder by clinicians in the community would be positively related to aggressive acts directed towards self and others. We found that, in this sample, many parents reported that their children/adolescents had both persistent and morbid fear-of-harm anxieties and severe overt aggressive behaviors. In addition, parents of children/adolescents with high fear-of-harm were much more likely to report that their children made frequent suicide threats.

4.1. Age and sex associations with aggressive behavior

The fairly strong association between age and target of aggressive behavior is worthy of note. The parents of the younger children in the study sample reported that the target of aggressive behaviors was more likely to be other children rather than self, a pattern reversed in the report of parents of older children. These data may reflect socialization processes resulting in the child's redirecting aggression toward the self away from other children (presumably due to intervention by parents/teachers and other adults). However, because the study data are cross-sectional only, we cannot determine whether such a target-shift-with-age occurred in these children/adolescents.

The lack of association between sex and parent report of frequent and intense aggressive behaviors, either directed towards self or towards others, was somewhat contrary to expectation. We had expected that girls would be more likely to be reported to engage in aggressive acts towards self and boys more likely to be reported to direct aggressive acts towards others. In fact, neither expectation was supported in the data.

4.2. Clinical implications

If replicated, these findings may have important implications for the diagnosis and treatment of juvenile-onset bipolar disorder. A strong relationship between obsessive fear-of-harm and overt aggressive behavior could represent a potentially useful phenomenological feature of the disorder. The prescription of antidepressant medication, otherwise appropriate to treat obsessive fears, may be reconsidered for an intensely fearful, aggressive child with abrupt, rapid mood changes, in light of recent evidence of possible induction of manic symptoms, psychosis, or exacerbation of aggressive behavior (Faedda et al., 2004). Suicide risk might be closely monitored in such children.

4.3. Research implications

For researchers, the relationship between fear-of-harm and aggression may generate hypotheses about the neurobiological underpinnings of juvenile-onset bipolar disorder. Recent findings suggest that the perception of a fearful signal and its differentiation from a new, but emotionally content-free stimulus is affected by cortico-amygdala and autonomic activity

(Williams et al., 2004). Studies using positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) in humans have provided evidence that the amygdala, implicated in impaired fear conditioning, responds to social cues, such as angry and fearful facial expressions, perhaps more strongly, in fact, than to fearful situations or events (Morris et al., 1996; Hariri et al., 2002, 2003). Facial expressions of fear and anger have been found to result in significant increases in amygdala activity, even when the faces are unattended or presented briefly and masked (Bishop et al., 2004). Subtle anomalies in a neural circuit encompassing the amygdala may predispose to perturbed encoding of fearful faces and the inability to correctly process and respond to novel stimuli, including, and perhaps most importantly, social cues. Bipolar subjects may be especially vulnerable to this impairment.

4.4. Study limitations

Child report data using the CYBOCS, which has developmental adaptations generally deemed more appropriate for children, would have strengthened this report, as parents in general do not report as accurately on their children's internalizing behaviors. However, the practicality of assembling child report data from children of a wide range in age and from a sample size equivalent to the one reported here has been a thorny issue for many researchers. Similarly, clinician diagnoses, possibly influenced by the presentation of aggressive behavior, have not yet been adequately validated using conventional research diagnostic methods. The effort to address these limitations, using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime system (K-SADS P-L) with both parent and child, is currently underway.

4.5. Summary

We report a very strong relationship between parent-reported obsessive fear of harm and parent-reported aggressive behavior and frequent suicide threats in children diagnosed with bipolar disorder by a clinician. We believe that this initial evidence of a possible phenomenological feature of pediatric bipolar disorder warrants further research.

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DIAGNOSING BIPOLAR VS. ADHD

By Dr. Charles Popper

Similarities

Both disorders share many characteristics: impulsivity, inattention, hyperactivity, physical energy, behavioral and emotional lability (behavior and emotions change frequently), frequent coexistence of conduct disorder and oppositional-defiant disorder, and learning problems. Motor restlessness during sleep may be seen in both (children who are bipolar are physically restless at night when "high or manic",though they may have little physical motion during sleep when "low or depressed"). Family histories in both conditions often include mood disorder. Psychostimulants or antidepressants can help in both disorders (that is, depending on the phase of the bipolar disorder). In view of the similarities, it is not surprising that the disorders are hard to tell apart.

Differences

So what features can help in distinguishing these two disorders? Some distinctions are obvious.

1. Destructiveness may be seen in both disorders but differs in origin. Children who are ADHD often break things carelessly while playing ("non-angry destructiveness"), whereas the major destructiveness of children who are bipolar is not a result of carelessness, but tends to occur in anger. Children who are bipolar may exhibit severe temper tantrums, during which they release manic quantities of physical and emotional energy, sometimes with violence and property destruction.

2. The duration and intensity of angry outbursts and temper tantrums in the two disorders differs. Children who are ADHD usually calm down within 20-30 minutes, whereas children who are bipolar may continue to feel and act angry for over 30 minutes and even for 2-4 hours. The physical energy that a child with ADHD "puts out" during an outburst of anger could be mimicked by an adult who tries to "enact" the tantrum, whereas the energy generated by angry children who are bipolar could not be imitated by most adults without reaching exhaustion within a few minutes.

3. The degree of "regression" during angry episodes is typically more severe for children who are bipolar. It is rare to see an angry child who is ADHD display disorganized thinking, language, and body position, all of which may be seen in angry bipolar children during a tantrum. Children who are bipolar may also lose memory of the tantrum.

4. The "trigger" for temper tantrums is also different in these disorders. Children who are ADHD are typically triggered by sensory and affective overstimulation (transitions, insults), whereas children who are bipolar typically react to limit-setting (i.e., a parental "NO") and conflict with authority figures. A child who is bipolar will often actively seek this conflict with authority.

5. The moods of children who have ADHD or bipolar disorder may change quickly, but children with ADHD do not generally show dysphoria (depression) as a predominant symptom. Irritability is particularly prominent in children who are bipolar, especially in the morning on arousal. Children with ADHD tend to arouse quickly and attain alertness within minutes, but children with mood disorders may show overly slow arousal (including several hours of irritability or dysphoria, fuzzy thinking or "cobwebs", and somatic complaints such as stomach aches and headaches) upon awakening in the morning.

6. Sleep symptoms in children who are bipolar include severe nightmares (explicit gore, bodily mutilation). Additional information on the specific content of these dreams and why children do not freely reveal these dreams is available in another article by Charles Popper (Diagnostic Gore in Children's Nightmares). Children who are ADHD mainly show difficulty going to sleep, whereas children who are bipolar are more apt to have multiple awakenings each night or have fears of going to sleep (both of which may be related to the dream content described above).

7. The ability to learn in children who are ADHD is often compromised by the coexistence of specific learning disabilities, whereas learning in children who are bipolar is more likely compromised by motivational problems. On the other hand, children who are bipolar are more able to use motivation to overcome inattention; they can stay tuned to an awesome TV show for long periods of time, but children who are ADHD (even if interested) may not stay involved, follow the plot or even stay in the room (especially during commercials).

8. Children who are bipolar often show giftedness in certain cognitive functions, especially verbal and artistic skills (perhaps with verbal precocity and punning evident by age 2 to 3 years).

9. In an interview room, children who are bipolar often demonstrate dysphoric, rejecting, or hostile responses during the first few seconds of meeting. Children who are ADHD, on the other hand, are more likely to be pleasant or at least non-hostile at first meeting, and if they are in a noisy location, they may immediately show symptoms of hyperactivity or impulsively. Children who are bipolar are also often "interview intolerant". They try to disrupt or get out of the interview, ask repeatedly when the interview will end, or even insult the interviewer. The child who is ADHD, on the other hand, may get frustrated, bored, or more impulsive, but usually without direct challenging the interview or the interviewer.

10. The misbehavior of children who are ADHD is often accidental. If they crash into a wall (or a limit or an authority figure), it is often due to oblivious inattentiveness. The child who is bipolar, in the other hand, is more likely to crash into a wall with intent, for the sake of challenging its presence, Children who are bipolar are highly aware of "the wall" and are sensitive to ways of creating the biggest feeling of impact or challenge to it.

11. The child who is ADHD may stumble into a fight, whereas the child who is bipolar will look for a fight and enjoy the power struggle. While a child who is ADHD may engage in self-endangering behavior without noticing the danger, the child who is bipolar enjoys the danger and seeks it out. The child who is bipolar is intentionally dare-devilish (yet needle phobia is quite prevalent). In general, the danger-seeking is grandiosity ("I'm invincible") in the child who is bipolar and inattentiveness in the child who is ADHD.

12. In the child who is bipolar, danger-seeking grandiosity, energized giggling, and sexual hyperawareness may be seen early in the preschool years, and persist into adolescence and adulthood.

13. The natural course of ADHD is chronic and continuous, but tends toward improvement. There may be periods of worsening, however, during situational or developmental stress, or if a coexisting conduct disorder worsens. Children with bipolar disorder may or may not show clear behavioral episodes or cycles, but they do tend to exhibit increasingly more severe or dramatic symptoms over the course of years, particularly as the child becomes larger and the impulsivity becomes more difficult to contain.

14. Children with ADHD do not exhibit psychotic (thoughts and behavior reveal a loss of contact with reality) symptoms unless thy have coexisting psychotic depression, preschizophrenia, a drug-induced psychosis, a psychotic grief reaction. Children with bipolar disorder may, on the other hand, exhibit gross distortions in perceiving reality or in interpreting affective (emotional) events. They may even exhibit paranoid-like thinking or openly sadistic impulses.

15. Lithium treatment generally improves bipolar disorder but has no or little effect on ADHD.

The Coexistence of ADHD and Bipolar Disorder

Children may have ADHD, bipolar disorder, or unipolar disorder (depression), and some children have a combination of ADHD and bipolar disorder or ADHD and unipolar disorder (depression). A child who has either bipolar disorder or unipolar disorder, but not ADHD, may be misdiagnosed ADHD, however, because both the bipolar and unipolar disorders may include symptoms of inattention, impulsivity, and even hyperactivity. There is concern that ADHD is being overdiagnosed and bipolar disorder underdiagnosed in the population of children.

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RESEARCH ARTICLE

Pediatric Mania: The Controversy between Euphoria and Irritability

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Abstract: Pediatric Bipolar Disorder (BD) is a highly morbid pediatric psychiatric disease, consistently associated with family psychiatric history of mood disorders and associated with high levels of morbidity and disability and with a great risk of suicide. While there is a general consensus on the symptomatology of depression in childhood, the phenomenology of pediatric mania is still highly debated and the course and long-term outcome of pediatric BD still need to be clarified. We reviewed the available studies on the phenomenology of pediatric mania with the aim of summarizing the prevalence, demographics, clinical correlates and course of these two types of pediatric mania. Eighteen studies reported the number of subjects presenting with either irritable or elated mood during mania. Irritability has been reported to be the most frequent clinical feature of pediatric mania reaching a sensitivity of 95–100% in several samples. Only half the studies reviewed reported on number of episodes or cycling patterns and the described course was mostly chronic and ultra-rapid whereas the classical episodic presentation was less common.

Few long-term outcome studies have reported a diagnostic stability of mania from childhood to young adult age. Future research should focus on the heterogeneity of irritability aiming at differentiating distinct subtypes of pediatric psychiatric disorders with distinct phenomenology, course, outcome and biomarkers. Longitudinal studies of samples attending to mood presentation, irritable *versus* elated, and course, chronic versus episodic, may help clarify whether these are meaningful distinctions in the course, treatment and outcome of pediatric onset bipolar disorder.

Keywords: Adolescence, bipolar disorder, cardinal symptoms, childhood, irritability, mania.

INTRODUCTION

Bipolar Disorder (BD) during childhood (age ≤12 years) and adolescence (age 13–18 years) was first described in antiquity by Aretaeus of Cappadocia (in 150 C.E), later reported by Esquirol in the early 1800s and then by Kraepelin and his contemporaries [1]. In recent times, converging evidence supports the notion that pediatric bipolar disorder is a highly morbid pediatric psychiatric disorder and that its prevalence is around 1.8% [CI 1.1–3.0] with similar rates in European and American countries [2].

Pediatric BD (PBD) is consistently and significantly associated with family psychiatric history of mood disorders [3], with increased risk in subjects who have a loaded (more than three members affected) and a multigenerational family history of mood disorder or a family history of mania [4, 5].

The diagnosis of PBD is complicated by a highly debated clinical picture and very high rate of comorbidity with other juvenile psychiatric disorders (attention deficit and hyper-activity, oppositional defiant and conduct disorders) with frequently overlapping symptomatology [6]. The clinical phenomenology and course of illness of PBD often differs from the classical episodic presentation of manic-depressive illness with clear cycling and periods of inter-morbid high functioning and instead often resembles the more severe and treatment resistant adult forms of BD with rapid-cycling course and mixed features with irritability, dysphoria and high risk of suicidal behaviors [1, 6, 7].

Age of onset can be identified during the preschool years with an age-dependent developmentally distinct symptomatology. Initial symptoms appearing during the preschool years often include irritability, moodiness, sleep

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Table 1. Phenomenology and course of pediatric mania.

Author and Year	Study Design; Type of Sample	N	Age (Range and Mean (SD))	Diagnosis	Dx criteria and Mania Symptoms Rating Scale	Manic Symptoms in BD Samples: Number of Subjects (%) or Symptoms Rating (Mean (SD))	Course Type (n, %of Sample)
Axelson, 2006 AGP [36]	Cross-sectional; clinical and community sample	438	7–18 years 12.7 (3.2) years	BDI 220 BD-NOS 116	DSM-IV; COBY criteria for BD-NOS	Irritability: BDI 84.5; BD-NOS 80.2 Elation: BDI 91.8; BD-NOS 81.9 Grandiosity: BDI 75.5; BD-NOS 62.1	N/A
Biederman, 2004 JAD [25]	Longitudinal, controlled; clinical sample	786	≤12 years 8.5 (2.3)	BD 172	DSM-III R DSM-IV	Irritability: 92%[a] Euphoria: 33% Euphoria + Irritability: 25% Euphoria without Irritability: 8%	Chronic: 80%[b] Episodic: 20%[c]
Birmaher, 2009 Bipolar Disorders [38]	Cross-sectional; clinical sample (out- and inpatients, advertisement)	264	A. ≤12 years 9.4 (1.5) B. >12 years; 14.5 (1.7) C. >12 years; 16 (1.3) [d]	A. BD 73 B. BD 101 C. BD 90	DSM-IV; COBY criteria for BD-NOS; K-MRS 13-item scale score	Elation: A 3.9(1.2); B 4.3(1.0); C 4.4(1.0) Irritability: A 4.1(1.5); B 4.3(1.4); C 3.7(1.4) Grandiosity :A 3.0(1.4); B 3.5(1.5); C 3.6(1.3)	N/A
Demeter, 2013 JAD [32]	Cross-sectional, outpatient clinical sample	535	4–17 years 10.5 (3.5)	BDI 290 BDII 17 BD NOS 155 CYCLO 73	DSM-IV K-MRS 13-item scale score	Irritability: BDI 4.7(1.7), BDII or NOS 3.3(1.6) [d] Elation: BDI 2.5(1.0), BDII or NOS 2.0(0.9) Grandiosity: BDI 2.6(1.3), BDII or NOS 2.1(1.1)	
Faedda, 2004 JAD [24]	Retrospective; outpatient clinical sample	82	3–17 years 10.6 (3.6)	BDI 43 BDII 33 CYCLO 6	DSM-IV	Irritability: 97.6; Angry: 92.7 Euphoric, grandiose: 59.8	UU-RC: 65.9 [e] Seasonal: 14.6 U-RC 12.2 RC: 7.4
Geller, 2000 JCAP [9]	Longitudinal; clinical outpatients sample	93	7–16 years 10.9 (2.6)	Pre-pubertal BD 53 Pubertal BD 40	DSM-IV [f]	Irritable mood: all 97.9; Pre-pub 96.2; Pub 100 [g] Elated mood: all 89.3; Pre-pub 88.7; Pub 90 Grandiosity: all 86.0; Pre-pub 84.9; Pub 87.5	UU-RC: all 77.4; Pre-pub 81.1; Pub 72.5 [e] U-RC: all 9.7; Pre-pub 3.8; Pub 17.5
Geller, 2002 JCAP [10]	Longitudinal; clinical outpatients sample and random controls	238	7–16 years BD 10.9 (2.6) ADHD 9.7(2.0) HC 11.0 (2.6)	BD 93 ADHD 81 HC 94	DSM-IV	Irritable mood: BD 97.9; ADHD 71.6; HC 3.2 [h] Elated mood: BD 89.3; ADHD 13.6; HC 0.0 [g] Grandiosity: BD 86.0; ADHD 4.9; HC 1.1 [l]	UU-RC: BD 77.4 U-RC: BD 9.7
Hunt, 2009 JCAP [31]	Retrospective; clinical sample (out- and inpatients, advertisement)	361	7–16 years 12.5 (3.3)	BDI 226 BDII 20 BD NOS 115	DSM-IV; COBY criteria for BD-NOS	Irritability only: 10.0 Elation only: 15.0 Irritability + Elation: 75.1	
Hunt, 2013 JCP [35]	Longitudinal (4 years follow-up); clinical sample (out- and inpatients, advertisement)	309	7–16 years 10.5 (2.8)	BD 309	DSM-IV; COBY criteria for BD-NOS	Irritability only: 9.7 Elation only: 13.6 Irritability + Elation: 76.7	- All groups showed a significant decrease in severity of irritability and elation score during follow-up. - Irritable only youth were at similar risk for mania but at greater risk for depression compared with elated-only youth and youth who had both irritability and elation symptoms.

(Table 1) contd….

Author and Year	Study Design; Type of Sample	N	Age (Range and Mean (SD))	Diagnosis	Dx criteria and Mania Symptoms Rating Scale	Manic Symptoms in BD Samples: Number of Subjects (%) or Symptoms Rating (Mean (SD))	Course Type (n, %of Sample)
Luby, 2006 Developmental Psychopathology [26]	Longitudinal; community-based sample	301	3–6 years	BD 26 MDD 37 Disruptive 65 HC 173	DSM-IV; Subjects selected using PAPA (Preschool Age Psychiatruc Assessment) to be included in one of the 4 groups	Irritability: 97 Elation: 72 Grandiosity: 80	
Masi, 2006 Biological Psychiatry [30]	Longitudinal; naturalistic clinical sample	136	7–18 years Episodic: 14.5 (2.5) Chronic: 12.3 (2.9)	BD 136	DSM-IV	Irritable group (no euphoria): 44.9[h] Elated group (with and without irritability): 55.1	Episodic-RC: 56.6[i] Chronic: 43.4
Masi, 2012 JCP [39]	Longitudinal; clinical sample	282	7–18 years BD+ADHD: 12.5 (2.9) BD+ANX: 14.6 (2.6) BD only: 14.6 (2.6)	BD+ADHD 49 BD+ANX 76 BD only 52	DSM-IV	Irritable mood: [l] BD+ADHD: 65 BD+ANX: 29 BD only: 42	Chronic course: [l] BD+ADHD: 67 BD+ANX: 25 BD only: 42
Rucklidge, 2008 Bipolar Disorders [52]	Retrospective; clinical sample	82	13–17 years 15.7 (1.55)	BD 25 ADHD 29 HC 28	DSM-IV; WASH-U-KSADS	Irritability: 76 Elated mood: 68 Grandiosity: 68	
Scheffer, 2004 JAD [28]	Retrospective; clinical sample	31	2–5 years	BD 31	DSM-IV; Young mania Rating Scale	Irritability: 100 Elated mood: 93 Grandiosity: 81	
Staton, 2008 JAD [53]	Cross-sectional; clinical sample	130	3–17 years 11.6 (0.00)	BD 130	DSM-IV	Elated mood: 81 Grandiosity: 91 Rage attacks: 49 (no report on irritability)	UU-RC: 52 (ultradian cycling) Chronic: 22
Tillman, 2004 AJP [27]	Longitudinal; clinical outpatients sample	93	7–16 years 10.9 (2.6) at baseline	BD 93 during current manic or mixed episode	DSM-IV	Irritable mood: 98 [m] Elated mood: 89 Grandiosity: 86	
Wozniak, 1995 JAACAP [7]	Cross-sectional; clinical sample	291	≤ 12 years 8.7 (2.3)	BD 43 ADHD 164 Non-ADHD 84	DSM-III-R; K-SADS-E	Irritability: 77% Euphoria: 5% Euphoria+Irritability: 9%	Chronic: 84% Episodic: 16%
Wozniak, 2005 Biological Psychiatry [20]	Cross-sectional, outpatient clinical sample	86	4–17 years	BD-I 86	DSM-IV; K-SADS-	Irritability only: 49%[n] Euphoria only: 6% Euphoria+Irritability: 45%	

Notes: a. N=36 BD subjects had available symptoms data; **b.** Chronic course included rapid cycling, multiple episodes lasting ≥ 12 months, or a single episode lasting ≥ 12 months; **c.** Episodic course refers to children with episodes lasting < 12 months or a single, brief episode; **d.** Group A children, group B adolescents with childhood-onset BD, group C adolescents with adolescent onset BD. **d.** Irritability score significantly decreased linearly with age ($p<0.01$) and was higher among BDI *vs.* BDII or NOS ($p<0.05$); **e.** course of illness: UU-RC (ultra-ultra-rapid cycling, >365 phases/year), URC (ultra-rapid cycling, 5–365 phases/year), RC (rapid cycling ≥ 4 phases/year); seasonal (exacerbations or recurrences with seasonal pattern for ≥ 2 consecutive years); **f.** Subjects needed to have current DSM-IV mania or hypomania with elated mood and/or grandiosity as one criterion; **g.** The rates of irritability, elated mood, and grandiosity were not significantly different between pre-pubertal and pubertal BD subjects; h. Irritable mood: BD *vs.* ADHD $\chi^2=13.6$, $p<0.001$; BD *vs.* HC $\chi^2=45.7$, $p<0.0001$; g. Elated mood: BD *vs.* ADHD $\chi^2=64.2$, $p<0.0001$; l. Grandiosity: BD *vs.* ADHD $\chi^2=61.0$, $p<0.0001$; BD *vs.* HC $\chi^2=36.6$, $p<0.0001$; h. Prevalently Elated group: distinctly elated mood, euphoria, and inflated self-esteem/grandiosity, with or without concomitant irritable mood, Prevalently irritable group: irritability and dysphoria but no prominent elated mood.; **i.** *Episodic course*: episodes lasting at least 7 days, more frequently superimposed on a less severely impaired baseline, fulfilling the adult diagnostic criteria *for rapid cycling BD (>4 episodes/year)*. In subjects with *chronic course*, the duration of the illness was *at least 6 months*, but usually the subjects remained clearly symptomatic for 1 or 2 years. The Episodic course was more frequent in patients with elated mood, while Chronic course was more frequent in patients with irritable mood; **l.** BD subjects with comorbid ADHD had a *prevalent chronic course and irritable mood*, had a greater clinical severity and functional impairment, had a manic/ mixed index episode, had a higher risk of conduct disorder, and were more resistant to treatments, according to the CGI-Improvement scores ($P < .0001$); **m.** Mania was defined by DSM-IV criteria, with at least one of the two cardinal symptoms of mania elated mood and/or grandiosity. Table **1** shows the prevalence of symptoms reported by parent only or child only or both informants; **n.** No difference were found between Irritable only *vs*. Irritable+Elated subjects in the rate of mania symptoms with the exception of "increased activity at school" which was higher in the children that had both irritability and euphoria.

disturbances and hyperactivity. Course pattern is mostly rapid or ultra-rapid with frequent mood shifts during a same day, whereas the classical episodic course is less common during juvenile years [1, 7-10].

Pediatric onset of BD is associated with elevated risks for substance abuse and addiction, anxiety, conduct and antisocial disorders, with high levels of morbidity and disability, as well as an increased risk of suicide [11-13]. Reported latency between initial affective symptoms and a first major affective episode in BD is 8–12 years, with up to another 9 years from a first affective episode to initiation of appropriate mood-stabilizing treatment [14-16].

More research is needed to identify early manifestation of pediatric mania in the youngest individuals, improve its differential diagnosis with other juvenile disorders such as ADHD and delineate the potential predictors of diagnostic stability and continuity between pediatric and adult bipolar disorder.

Clinical Picture of Pediatric Mania

According to the Diagnostic and Statistical Manual for Mental Disorders (DSM V) [17], mania can be characterized by a severe and impairing abnormal mood state that is either euphoric or irritable. These two sides of mania have been observed and well described in clinical descriptions of bipolar children and adolescents. Euphoria is characterized by an elated, high-energy state with grandiose feelings and ideas. Children in this state appear cheerful, over-the-top funny, sometimes hilarious, and frequently show immature-giddy behaviors that are difficult to be contained by both parents and peers. These children may also be grandiose with over-confidence, taking on unrealistic projects and defying adult authority to an extreme degree [18].

The other mood state of mania is characterized by irritability. In adult patients, clinicians frequently diagnose impairing mixed states (or dark mania) with extreme irritability. In children or adults, these mood states can appear as nastiness, blaming, demanding, whining, or viciousness, characterized by explosive rages that can be physically abusive, destructive and dangerous [18]. Irritability, though highly debated as characteristic of many disorders, is as an important manic feature. When occurring frequently and intensely, the quality and quantity of irritability can distinguish a bipolar diagnosis. Even in the presence of other classic symptoms of melancholy and euphoria, irritability is often the most impairing aspect of the clinical picture and often forms the chief complaint for referral to psychiatric services. Irritability without euphoria has been reported as the most common mood presentation in children presenting with PBD [7], with high levels of impairment and morbidity and is often associated with impulsive and reckless behaviors, violent gestures and impulsive suicidal thoughts, threats and behaviors [7, 19-21].

Mixed states with high levels of irritability have been commonly reported in adults with bipolar disorder. For these patients, psychosis, aggressive behaviors and psychomotor agitation can be a primary cause of hospitalization [6].

We reviewed the available studies on the phenomenology of pediatric mania with the aim of summarizing the prevalence, demographics, clinical correlates and course of these two types of pediatric mania.

METHODS

A Pubmed literature search using key terms including pediatric mania/bipolar disorder, childhood onset mania/ bipolar disorder, juvenile onset bipolar disorder was conducted. From the identified articles, additional articles were noted in the reference sections. Of the articles, eighteen were identified which reported the number of subjects with either irritability or elation as the presenting mood symptom in samples of subjects younger than age 18 years old.

RESULTS

Eighteen studies reporting the number of subjects presenting with either irritable or elated mood during mania or informing about the rating of manic symptoms were identified and summarized in Table **1**. Information reported in the Table include the study design, the type of sample with age range and mean, the prevalence of irritability, elation and grandiosity symptoms in each sample as available and information on the course pattern of the disorder (Table **1**). While all studies report high rates of both euphoria and irritability, 14 of the 18 studies report irritability as a predominant mood symptom. For studies which reported euphoria, irritability and the combined state, the combined state of 'euphoria+irritability' is the most common mood presentation, but these studies varied in their methodology of establishing the mood state, with some asking for a week or longer of the mood state to code it while others ask for a week or longer of either mood state and code the combined condition if both abnormal moods are present at all. Eight studies provide information on cycling patterns, with rapid cycling or chronic course most commonly reported.

DISCUSSION

Clinical Symptoms: Irritability Versus Elation

Our report summarizing the predominant mood presentation in youth with mania supports the importance of irritability in diagnosing pediatric bipolar disorder. Some investigators [10, 22, 23] have argued that euphoria (as opposed to irritability) is unique to bipolar disorder and therefore should be considered the defining mood disturbance of bipolar children. Other authors (see Table **1**) have reported that irritability may be the most common abnormal mood associated with pediatric bipolar disorder [7, 9, 10, 20, 21, 24-27], with sensitivity reaching 100% for mania in some samples [28], and therefore should be considered to be a bona fide symptom of mania. Findings from two meta-analysis support this latter view and found high rates of irritability in all age groups with mania suggesting that irritability may be a marker of mania in children and that euphoria and grandiosity are usually less common in children than in adults [1, 29].

The prevalence of irritable mood varies in relation to the inclusion criteria of the analyzed sample. In fact in some reports bipolar subjects had been included only if presenting with one of the two cardinal symptoms elation or grandiosity. In these samples the prevalence of irritability as associated mood symptom can be low (29% in the bipolar sample with anxious comorbid disorder reported by Masi and colleagues [30]) but usually is reported to be present in more than 90% of the cases in association with euphoria [9]. Some samples required 'a week or longer' of the mood state to be coded as present while others required a week or longer of abnormal mood and coded elation or irritability if present at all during this week. Some studies reported a severity rating for these symptoms.

Some authors reported that pediatric subjects with irritable mania are significantly younger than those presenting euphoric mania [30, 31] and that the irritability score significantly decreased linearly with age [32]. Accordingly, retrospective studies found that irritability, mood lability and impulse dyscontrol may be the predominant psychopathological features of pediatric bipolar disorder at onset [33, 34]. A possible explanation of this finding might be that irritability is generally a highly prevalent psychopathological feature during pediatric age.

Moreover, several independent laboratories have shown that bipolar youth with predominantly irritable mood do not significantly differ from those presenting with euphoric mood in their profile of symptoms of mania, measures of social functioning and long-term outcome [20, 35]. Some authors suggest that patterns of comorbidity may be different with prevalently irritable subjects, who have higher rates of comorbidity with ADHD and other externalizing disorders and a chronic course, whereas euphoric manic subjects more frequently show an episodic course and a comorbid anxiety disorder [30].

Course Pattern: Episodic Versus Rapid and Ultra-rapid Cycling

Despite debate regarding chronicity and episodicity in pediatric mania, only half the studies reviewed reported on number of episodes or cycling patterns. The duration of manic episodes can range from brief tantrum-like affective storms lasting minutes or hours to longer episodes persisting for several days or months. The existence of very short episodes of mania lasting minutes or hours and the consequent identification of a ultra-ultra-rapid course pattern of pediatric bipolar disorder characterized by more than 365 cycles per year (at least one mood shift per day) or ultra-rapid course pattern (with 5–365 cycles per year) is another highly debated point among authors analyzing pediatric mood disorder phenomenology [24].

Current DSM-V criteria (and also the previous DSM-IV criteria) for mania include the *duration criteria* of at least 4–7 consecutive days of abnormal mood state respectively for hypomania and mania [17]. For this reason, many juvenile bipolar subjects are currently classified as Bipolar Not Otherwise Specified (NOS) for which several research groups have operationalized symptom criteria aimed at classifying brief and severe manic and hypomanic episodes [36].

Explosive temper outbursts that are considered by many authors as a common manifestation of short episodes of irritable mania, have been included in DSM-V as the new syndrome Disruptive Mood Dysregulation Disorder (DMDD) that is classified among unipolar depressive mood disorders with the aim of differentiating subjects presenting with chronic *versus* episodic irritability.

This new category stands in contrast to the very high rate of ultra-ultra-rapid and ultra-rapid cycling bipolar course characterized by ultradian mood cycling described by several authors as the most common presentation of bipolar disorder during pre-pubertal and early adolescent age [7, 9, 24]. In fact, 65–80% of juvenile bipolar subjects were reported to present an ultra-ultra-rapid course pattern, followed by the ultra-rapid and rapid course, whereas the classical episodic presentation of depressive and manic episodes is more rare in juvenile ages [7, 24, 25]. Moreover several longitudinal course studies showed that bipolar patients spend most of the time suffering from a sub-syndromal mixed and depressive symptomatology, miming the chronic mood dysregulation [35, 37, 38].

Masi and colleagues reported that even patients with an episodic pattern showed a rapid cycling course (>4 episodes per year) and that a chronic course was identified in 43% of a bipolar juvenile sample [30]. Patients with a chronic course were reported to be younger, mostly irritable when manic, with an earlier onset of BD and with more comorbid externalizing disorders when compared to juvenile subjects with an episodic bipolar disorder [39].

Long-term Outcome: Mania Versus SMD/DMDD

Findings from retrospective studies of adult bipolar disorder patients indicate that between one-third to more than half had experienced early psychopathological symptoms during childhood or adolescence [16, 34, 40]. Perlis *et al*. reported that 65% of a large (N=983) sample of bipolar adults reported mood symptoms starting in the prepubertal (28%) or adolescent years (37%) [41]. These reports suggest that pediatric mania can and does persist into the adult years.

Typical reported early features include mood swings, early depressive symptoms, dysregulated mood, activity and sleep patterns, irritability and disordered behaviors including aggression [33, 42]. Longitudinal, including high risk family studies, are consistent with retrospective studies in identifying that sub-syndromal depressive and hypomanic symptoms often precede bipolar disorder by several years [33, 43] with a reported latency between initial affective symptoms and the first identified major affective episode in BD between 8 to 12 years [34], with another 8 to 10 years from the first affective episode to the initiation of an appropriate mood-stabilizing treatment [14-16]. An important clinical and prognostic aspect of undiagnosed and untreated early BD is an elevated risk of substance misuse, anxiety disorders as well as conduct and antisocial disorders, with high levels of morbidity, disability and suicide [12, 44].

Also, adult mood disorders with a juvenile onset are more severe and more recurrent than similar illnesses starting in adult years [12, 15, 41]. Particularly, childhood onset BD was associated with a greater number of episodes, higher percent time ill, a higher risk of rapid cycling and more severe manic and depressive episodes [12, 41], as well as with greater rates of other psychiatric disorders, especially with comorbid anxiety disorders and substance abuse, with greater likelihood of suicide attempts and violent behaviors [41].

The fact that untreated and early onset bipolar disorder results in a worse clinical outcome highlights the importance of a closer linkage between pediatric and adult psychiatry, to clarify the natural history of childhood disorders by their outcomes and in order to predict the diagnosis, course and prognosis of adult mood disorders, with the possible aim of improving long term adult outcomes.

Some authors have reported findings strongly supporting continuity between pediatric and adult bipolar disorders. Geller and colleagues followed for 8 years 115 PBD-I subjects presenting on average at age 11 years with a manic or mixed episode [37]. At the end of the 8 year follow-up period, results showed that subjects spent 60.2% of the weeks in any mood episode and 40% of the weeks in manic episodes. Also, at the end of follow-up 54/115 subjects were 18 years or older and continue to have manic episodes in 44% of cases while 35% also had a comorbid substance abuse disorder, a rate that is similar to that found in adult BD-I subjects [37].

Wozniak and colleagues documented a highly persistent course of bipolar disorder in youth. These authors followed-up after 4 years 78 PBD-I subjects who were an average age of 13.4 years at intake. At the end of follow-up period, 73% of subjects continued to meet full diagnostic criteria for BD-I, 6.4% met criteria for sub-syndromal mania, 5.1% met criteria for major depressive symptoms (but not mania), 9% were euthymic but were taking mood-stabilizing medications, and only 6.4% were euthymic with no medications. This data indicates the importance of considering the full range of persistence in longitudinal samples beyond continued BP-I disorder in order to understand the extent of ongoing morbidity in this population [45].

Hunt and colleagues followed 309 BD subjects presenting a baseline with either irritability only (n=30), elation only (n=42) or irritability and elation (n=237) for 4 years. At the end of follow up most bipolar youth experienced both irritability and elation irrespective of history at baseline and irritable only youth were found to be at similar risk for persistence of mania compared to elated only or irritable and elated subjects. Few studies stratified follow up by the symptoms of irritability and elation or by chronicity versus episodic course, but in this study irritable only subjects experienced a greater depressive morbidity during follow-up than did subjects who were both irritable and elated [35].

With respect to the longitudinal course of the new DSM-V diagnostic category of Disruptive Mood Dysregulation Disorder, a disorder of irritability, some studies have reported that rates of conversion from severe, non-episodic irritability to bipolar disorder are very low [46] and that children with chronic irritability are at risk to develop unipolar depressive and/or anxiety disorders in adulthood [47, 48]. Brotman and colleagues followed prospectively children meeting criteria for severe mood dysregulation until age 18 and they found that severe mood dysregulated youth were significantly more likely to be diagnosed with a depressive disorder at age 18 when compared to youth with no severe mood dysregulation. Similarly, Copeland and colleagues (2014) reported that young adults with a history of DMDD had elevated rates of anxiety and depression relative to comparison subjects with no history of DMDD and that participants with a history of DMDD were more likely to have adverse health outcome including police contact. The low rates of bipolar disorder in these studies may not be surprising since the exclusionary criteria for DMDD list any symptoms of mania beyond irritability. Axelson and colleagues suggested that DMDD could not be distinguished from oppositional defiant disorder and conduct disorder and was not associated with mood disorders at all [49]. However, since the onset of a major depressive disorder by age 18 has been reported to be a strong predictor of later conversion to bipolar disorder [33, 50] and since, similarly, a unipolar major depressive disorder with associated antisocial behaviors and great functional impairment has been reported to have a high risk to switch to bipolar disorder [42, 51], it seems likely that bipolar disorder would be an outcome of at least some subset of childhood DMDD cases. While the longitudinal course of illness should be taken into account as very important in differentiating complicated clinical pictures in childhood, the results of studies reporting a low long-term outcome rate of bipolar disorder among DMDD subjects should be taken with caution and seen in light of the above discussed limitations.

SUMMARY

Irritability has been reported to be the most frequent clinical feature of pediatric mania reaching a sensitivity of 95–100% in several samples (Table **1**). Despite this high sensitivity, irritability has been criticized as a nonspecific symptom because it could be a feature of other juvenile psychiatric disorders notably depression and oppositional defiant disorder. Nevertheless, some authors have reported that the quality and quantity of irritability observed in some children may be uniquely associated with mania. This irritability is extremely severe with aggression and outbursts and substantially distinct from the irritability seen in other psychiatric conditions. Taken together, this suggests that irritability as a symptom *per se* may not be pathognomonic of bipolar disorder, but that the severe form of irritability described in children with bipolar disorder may be considered as an equally meaningful mood criterion for pediatric mania [19] as that of euphoria. Attention to the heterogeneity of irritability could guide future research aimed at differentiating distinct subtypes of pediatric psychiatric disorders with distinct phenomenology, course, outcome and biomarkers. Longitudinal studies of samples attending to mood presentation, irritable *versus* elated, and course, chronic versus episodic, may help clarify whether these are meaningful distinctions in the course, treatment and outcome of pediatric onset bipolar disorder.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Recognizing and Managing Bipolar Disorder in Children

Janet Wozniak, M.D.

Bipolar disorder affects people of all ages, including preschool-aged children. Two major difficulties in diagnosing children with bipolar disorder are its overlap with attention-deficit/hyperactivity disorder (ADHD) and its developmentally distinct presentation from that in adults, with high rates of irritability, chronicity, and mixed states. Comorbid conditions are common in bipolar disorder and, in addition to ADHD, include depression, anxiety disorders, oppositional defiant disorder, and conduct disorder. Family studies have helped to confirm the validity of bipolar disorder in children. In terms of treatment, children do not appear to respond well to conventional mood stabilizers alone. However, using an atypical antipsychotic either alone or in addition to another mood stabilizer has shown utility in treating manic symptoms, depression in mixed states, and aggression. Amphetamine salts have been helpful in treating bipolar children with comorbid ADHD, but no data are available on treating comorbid depression in bipolar children. Because childhood-onset mania is commonly chronic rather than episodic, highly comorbid, and characterized by high rates of irritability, future clinical trials should examine the overlap of mania with other disorders in children to determine routes to accurate diagnosis and treatment. *(J Clin Psychiatry 2005;66[suppl 1]:18–23)*

Converging evidence suggests that bipolar disorder can commonly occur in very young children but may be difficult to diagnose. One of the main challenges of diagnosing bipolar disorder in children and adolescents is its high comorbidity with other psychiatric disorders, particularly attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and depression. The overlap of bipolar disorder with ADHD has caused considerable confusion and debate in the child psychiatry field. ADHD is a common disorder affecting 5% to 7% of children,[1] but some of the core symptoms of ADHD, such as distractibility, physical hyperactivity, and talkativeness or pressured speech, directly overlap with the diagnostic criteria for mania. The other main challenge of diagnosing bipolar disorder in children and adolescents has been its distinct presentation from that commonly thought to occur in adults.

OVERLAPPING ADHD AND OTHER PSYCHIATRIC DISORDERS

Many studies[2–7] have demonstrated that children and adolescents with a current diagnosis of mania or bipolar disorder have symptoms that overlap with ADHD, a relationship that appears to be a function of age at onset of bipolar disorder. Among children 12 years old or younger, the overlap of bipolar disorder with ADHD appears almost universal (ranging from 73% to 98%).[2,4,8] In the adolescent-onset form of bipolar disorder (in adolescents ≥ 13 years old), the overlap is lower (ranging from 57% to 74%).[4,5,8,9]

Increasingly, adults are presenting with bipolar disorder comorbid with ADHD.[3,10] Some of these adults report an early age at onset of their bipolar disorder. For example, a recent report[11] of data from the first 1000 participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that 20.4% of adults with very early onset bipolar disorder (onset when they were ≤ 13 years old) had comorbid ADHD and bipolar disorder. Even more adults date the start of their bipolar disorder to the adolescent years.[12–14] Overall, adults with an earlier age at onset and a higher level of comorbidity have worse functioning, which is similar to outcomes seen in children with bipolar disorder. Increasingly, adult data of combined bipolar disorder and ADHD have supported findings in children,[15] demonstrating that bipolar disorder plus ADHD may be a distinct genetic subtype and an important part of the heterogeneity of bipolar disorder in general.

Data over time and across centers have revealed a pattern of bipolar presentation in children that is remarkably consistent.[2,8,16] In our 1995 study,[2] for example, we reported that although children meeting diagnostic criteria for mania frequently met criteria for ADHD (98%), ADHD children less frequently met criteria for mania (20%).

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Table 1. Rates of Additional Psychiatric Disorders Found in Children With Mania and ADHD[a]

	Manic Children (N = 43)		ADHD Children (N = 164)		Non-ADHD Controls (N = 84)		Significance[b] (df = 2)
Psychiatric Diagnoses	N	%	N	%	N	%	p Value
Major depression	37	86[c,d]	63	38[d]	3	4	< .001
Psychosis	7	16[c]	3	2	NA	0	< .001
Conduct disorder	16	37[c,d]	24	15[d]	0	0	< .001
Oppositional defiant disorder	38	88[c,d]	78	48[d]	3	4	< .001
Multiple anxiety disorders (≥ 2)	24	56[c,d]	43	26[d]	1	1	< .001
Overanxious disorder	21	49[c,d]	39	24[d]	2	2	< .001
Separation anxiety disorder	19	44[c,d]	36	22[d]	4	5	< .001
Agoraphobia	14	33[c,d]	24	15[d]	1	1	< .001
Panic disorder	4	9[c,d]	1	0.6	0	0	< .001
Social phobia	10	23[d]	26	16[d]	1	1	< .001
Simple phobia	8	19	28	17	7	8	.138
Obsessive-compulsive disorder	5	12[d]	7	4	0	0	.008
Tic disorders	11	26[d]	49	30[d]	5	6	< .001

[a]Reprinted with permission from Wozniak et al.[2]
[b]Overall comparisons between manic, ADHD, and non-ADHD control by χ^2 analyses or by analysis of variance.
[c]$p \leq .01$ versus ADHD by χ^2 analysis or by Fisher protected least significant difference.
[d]$p \leq .01$ versus non-ADHD control by χ^2 analysis or by Fisher protected least significant difference.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NA = not applicable.

Compared with children with ADHD without mania, children with ADHD and mania had more comorbid psychiatric disorders, such as depression, oppositional defiant disorder, and multiple anxiety disorders (Table 1).

Children with manic symptoms appear to have a high rate of depression.[2] About one third of children present with depression first, one third present with mania first, and about one third present with a mixed state (manic and depressed symptoms simultaneously apparent). Children with bipolar disorder not only have high rates of depression, they also tend to meet criteria for severe depression, with high rates of suicidality as well as suicide attempts, and often require hospitalization for suicidal behavior as well as their aggressive behaviors.[17] Data[18] on adolescent suicide show that those who completed suicide had higher rates of bipolar disorder, especially mixed states, and a higher rate of comorbid ADHD than those who attempted suicide.

Besides depression, children with mania also have a high rate of oppositional defiant disorder.[2] Parents of bipolar children with oppositional defiant disorder or conduct disorder report high rates of all symptoms to severe degrees.[2,19] ADHD has long been known as a risk factor for developing conduct disorder; in one study,[20] 50% of youths with ADHD met criteria for conduct disorder at a 1-year follow-up. But, in our study,[2] children with mania had a rate of current comorbid conduct disorder more than twice that of the ADHD children. Because conduct disorder is a precursor to later adult antisocial behaviors and criminality, children with bipolar disorder are an important group to study from a public health perspective. Children with bipolar disorder also have high rates of anxiety disorders,[21,22] a bidirectional overlap with obsessive-compulsive disorder,[21,23] and, although understudied, autism.[24]

RECOGNIZING DEVELOPMENTALLY DISTINCT PRESENTATION

Age at onset of bipolar disorder in children varies widely and includes very young children (≤ 5 years old). Although the average age of referral to our clinic is 8 years, about 75% of parents report symptoms beginning during the preschool years. Consequently, most children who eventually receive treatment have already suffered an average of 3 to 4 years with either no treatment or inappropriate treatment for their mood disorder. The increasing recognition among clinicians that parents are describing bipolar disorder in their preschool children has led to more attention being paid to identifying and treating the disorder in these very young patients. Clinicians who identify bipolar disorder in young children must rely heavily on case reports in the literature to determine appropriate treatment.[25] Research studies, especially treatment studies in such young patients, are difficult to conduct and often met with resistance.

Investigations into the developmentally distinct presentation of bipolar disorder in children as opposed to adults have focused on atypical presentation and the need for developmentally sensitive assessment tools. Investigations that focus on presentation report that children tend to have higher rates of mixed states, higher levels of irritability as the presenting mood complaint, more chronicity, and a complex cycling pattern that lacks a recovery period or interepisode high functioning.[26,27] This atypicality has led to some debate as to whether children are presenting with bipolar disorder as seen in adults.

Investigations that focus on assessment methods report a need for developmentally sensitive questions to uncover the core symptoms of mania or bipolar disorder in children. The lack of an assessment tool that culls childhood

traits from mood disorders may be one of the reasons that childhood bipolar disorder has been overlooked in the past. For example, the presence of mood reactivity, moodiness, or even grandiosity has been considered, in many cases, to be a normal trait of childhood because children have less of a capacity than adults for affective regulation. Thus, efforts to validate an instrument specific to pediatric bipolar disorder are underway,[28] and pediatric prompts for use with psychiatric rating scales such as the General Behavior Inventory[29] and the Young Mania Rating Scale[30] are being developed. For instance, questions regarding hypersexuality could include additional prompts to parents regarding their children: "Does your child exhibit excessive interest in sexual matters or bodily functions and private body parts (more than other children his or her age)?" "Does your child seek out pornography or sexual content in the supermarkets or on the Internet?" "Does your child touch himself or herself on the genitals in public or touch others inappropriately?" These questions often elicit responses from parents that reveal aspects of increased sexual interest and activity in children that may not have been linked to the mood disorder. Questions about grandiosity are also being expanded to help identify children who overestimate their ability to do things and take excessive chances or act excessively boastful or bossy in ways that alienate others. In some children, increased oppositional and defiant behaviors toward authority figures may represent the grandiosity of mania.

In a recent case study, Tumuluru et al.[25] reported that 6 preschool-aged children who met the criteria for severe mania were admitted to a children's inpatient psychiatric unit. Irritability was readily observable but euphoric mood was not. Consistent with a previous report,[31] a strong family history of mood disorders as a predictor of bipolar illness was present in these preschool children. In addition, at some point, each child presented with ADHD symptoms and mood symptoms that impaired functioning similar to those found in older children. In another study, Wilens et al.[32] compared preschool-aged children and school-aged children in an outpatient psychopharmacology clinic and found that the younger children presented with all the same symptoms seen in the older children. These findings underscore the need for clinicians to overcome diagnostic prejudices and form developmentally sensitive questions that will help identify very young children with bipolar disorder.

At least one family study[15] confirms that mania presenting in children seems to be continuous with what we think of as bipolar disorder in adults. This study also confirms findings from a previous smaller pilot study[10] of 15 bipolar youths in 1995. This newer study[15] systematically assessed 107 manic children and adolescents with 298 first-degree relatives. Children who met criteria for mania had greater rates of familiality of mania than comparison groups of ADHD or control children, 14% versus 4%. About 40% to 50% of the manic children had a first-degree relative with bipolar disorder. This study also confirmed a pattern of cosegregation of bipolar disorder and ADHD, suggesting that combined bipolar disorder and ADHD may be a genetic subtype of bipolar disorder possibly with its own course, family history, and treatment responsivity. In other studies,[10,33] children with comorbid ADHD and mania were found to have greater family history of mood disorder compared with non–bipolar disorder ADHD children. These findings indicate the need for more specific genetic studies in the future.

As child and adolescent psychiatry professionals have become aware of and accustomed to the fact that children can present with severe mood symptoms that suggest bipolar disorder, the question has arisen as to whether there are particular cardinal symptoms that are more useful than others in making the diagnosis, especially in cases that might appear to be borderline. Proposed criteria[7,34] that could be useful in discerning genetically distinct groups include euphoria versus irritability, grandiosity, and evidence of clear cycling or episodicity. These particular characteristics have been proposed because euphoria and grandiosity are thought by some clinicians to be unique to mania with no overlap with other disorders. Irritability, on the other hand, is a presenting feature of depression as well as other disorders such as oppositional defiant disorder. Although irritability is not one of the criteria for a diagnosis of ADHD, it is thought of as a common correlate of ADHD. Other groups[35] have argued that the irritability of mania appears to be qualitatively and quantitatively distinct and can be a useful symptom in discerning manic children.

Our research group recently presented data[36] suggesting that stratifying by these proposed cardinal features does not predict a more familial form of pediatric bipolar disorder. In addition, the proposed cardinal features did not predict any difference in symptom presentation, course, age at onset, or patterns of comorbidity. Whether cardinal symptoms will become important in making the diagnosis of childhood bipolar disorder or not remains to be decided.

TREATING BIPOLAR DISORDER IN CHILDREN

Mood Stabilizers

Treatment studies in bipolar children have expanded in the past several years. Generally, conventional mood stabilizers—lithium, valproic acid, or carbamazepine—have low effect sizes in bipolar children. Kowatch et al.[37] reported that only about 40% of children and adolescents taking lithium, carbamazepine, or valproic acid responded to these medications. Wagner et al.[38] found similar low effect sizes in children and adolescents taking divalproex sodium, including a high dropout rate owing to side effects or ineffective treatment. However, increasingly, studies have examined whether combination treatment with these

various agents may lead to better outcomes. Results from the second phase of the study by Kowatch et al.[39] indicated that combined treatment led to a better outcome than using any 1 of the medications on its own (regardless of which 2 therapies were combined). Studies of the combination of 2 mood stabilizers (lithium and divalproex sodium)[40] or a mood stabilizer and an atypical antipsychotic (lithium and risperidone[41] or valproic acid and quetiapine[42]) have demonstrated superior efficacy to traditional mood stabilizers used alone.

Atypical Antipsychotics

Despite the lack of controlled trials in young patients, atypical antipsychotics, which have been found to have mood-stabilizing properties in adults, are increasingly used as first-line treatments in children and adolescents with bipolar disorder. Reasons for their increasing use include the observations that traditional mood stabilizers are associated with a long length of time required to stabilize bipolar children, difficulty in treating children with bipolar disorder,[43] the need for a large number of medications used in combination to stabilize youth, and high rates of relapse.[44] The atypical antipsychotics risperidone, olanzapine, quetiapine, and ziprasidone have been approved by the U.S. Food and Drug Administration (FDA) for use in adults with mania and are commonly utilized clinically in pediatric populations. In addition, the FDA recently approved aripiprazole for the treatment of acute bipolar mania, including manic and mixed episodes, in adults.

A chart review[45] of youths with DSM-IV bipolar disorder indicated a favorable response to risperidone. Of 28 juvenile patients who received risperidone, 82% showed improvement in mania and aggression, while 69% showed improvement in psychotic symptoms. Risperidone also demonstrated utility in reducing some of the depression presented in children with bipolar disorder in mixed states. Although a trial[46] of risperidone in children with subnormal IQ and conduct disorder did not specifically examine mood symptoms, a reanalysis[47] of this sample showed possible utility for mania and depression. These results lend support to the use of risperidone for pediatric mania. Olanzapine has shown utility for reducing manic symptoms in adults, and open research[48] has shown that olanzapine was useful in 20 bipolar children and adolescents. A multisite, double-blind, placebo-controlled trial of olanzapine in adolescents with bipolar disorder is under way.

Recommendation

The poor effect sizes and the need for combined treatments with the conventional mood stabilizers, as well as the more robust data that are starting to accumulate on the atypical antipsychotics, generally indicate that, in clinical settings, atypical antipsychotics should be considered first-line treatments for many cases of pediatric mania. Due to the substantial morbidity associated with pediatric-onset bipolar disorder, all of the mood stabilizers that are used in adult bipolar disorder are commonly used in clinical settings to treat children and adolescents despite the current void of scientific evidence to demonstrate their utility.[49]

TREATING COMORBID CONDITIONS

Treating comorbid conditions in young patients with bipolar disorder offers another challenge for clinicians. Little has been published on treating the ADHD symptoms that are frequently comorbid in children with bipolar disorder. A review[50] of our own patient charts showed that using ADHD medications in this group either made matters worse or had no effect if manic symptoms were not stabilized. However, after reducing manic symptoms in a bipolar child, adding treatment that is appropriate for ADHD can improve the complicated clinical picture. We found that the proportion of visits at which ADHD symptoms were rated as improved following initial improvement in manic symptoms was 7.5 times greater than before initial improvement of manic symptoms.

The clinical wisdom is to proceed with caution, but generally ADHD in and of itself carries so much morbidity that clinicians find themselves compelled to make attempts to treat the ADHD when the patient's mood is stable by adding a treatment for ADHD. Scheffer,[51] for example, showed that mixed amphetamine salts could be successfully used to treat ADHD in youth with comorbid ADHD and bipolar disorder after mood stabilization with divalproex sodium.

No studies of treating the depressive aspect of bipolar disorder in children exist. Given the morbidity associated with depression in bipolar disorder in adults and the recent concerns that have been raised regarding the serious side effects that can be associated with antidepressants in the pediatric population, treating depression in juveniles has become a matter of increasing concern.[52]

CONCLUSION

The overlap of bipolar disorder with other psychiatric conditions is common and includes depression, anxiety disorders, oppositional defiant disorder, and conduct disorder. Even children as young as preschool age can suffer from bipolar disorder. Treating young children is difficult because of the large number of medications they need in combination and the high rates of relapse. However, atypical antipsychotics and combinations of mood stabilizers have been found in some preliminary studies to be effective in treating manic symptoms, depression in mixed states, and aggression. Amphetamine salts have been helpful in treating bipolar children with comorbid ADHD in one preliminary report,[51] but no data are available on treating comorbid depression in bipolar children. Future

clinical trials should examine treatments that may be useful for treating not only the manic symptoms of bipolar disorder, but also the depressive phase and mixed states in children and the overlap of bipolar disorder with other psychiatric disorders.

Drug names: amphetamine/dextroamphetamine (Adderall and others), aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, aripiprazole, carbamazepine, divalproex, lithium, olanzapine, quetiapine, risperidone, valproic acid, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of pediatric bipolar disorder.

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