Diagnostic Characteristics of Child Bipolar I Disorder: Does the "Treatment of Early Age Mania (TEAM)" Sample Generalize?

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Objective: To examine the representativeness of a randomized controlled trial (RCT) sample versus one obtained by consecutive new case ascertainment, for subjects with child bipolar I disorder.

Method: Subjects (N = 247) were outpatients who participated in either the National Institute of Mental Health–funded Phenomenology and Course of Pediatric Bipolar Disorders study or the Treatment of Early Age Mania (TEAM) study. Both studies required that subjects have current DSM-IV bipolar I disorder (manic or mixed phase) and a Children's Global Assessment Scale (CGAS) score ≤ 60. All subjects had elation and/or grandiosity. Subjects in the Phenomenology study were obtained from 1995 to 1998 by consecutive new case ascertainment from designated pediatric and psychiatric facilities. Subjects in the TEAM RCT were recruited from media and community sources between March 2003 and March 2005. Assessment instruments included the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia, given separately to parents about their children and to children about themselves, and the CGAS. Logistic regression was used for comparisons.

Results: The TEAM and Phenomenology groups were similar in age (10.4 [SD = 2.3], 10.9 [SD = 2.3] years, respectively) and other demography. Both had long current episode duration (4.8 [SD = 2.4], 3.2 [SD = 2.3] years) and low lifetime use of any mood stabilizer (23.6%, 35.0%). Many mania symptoms and ultradian rapid cycling, psychosis, and suicidality were significantly more prevalent in the RCT sample.

Conclusions: Generalization of the RCT sample was supported, because only 7.8% of Phenomenology subjects did not fit the RCT criteria. Nevertheless, because the RCT subjects were more severely ill, it is unclear if treatment findings from the RCT will be applicable to children with less severe mania.

Clinical Trials Registration: ClinicalTrials.gov identifier NCT00057681 (TEAM study).

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One of the important questions in designing and interpreting intervention studies is whether they will generalize to real world practice.[1] Although there are a number of studies examining this issue in adult mood disorders,[2–9] there are, to our knowledge, no prior studies investigating the generalizability of treatment study results in child mood disorders. Even in adults, few studies have looked at this topic in the bipolar I disorder population.[2,3]

Two studies of adult bipolar I disorder found that 83.5%[2] and 55.3%[3] of comparison individuals would not have qualified for the randomized controlled trials (RCTs) due to exclusion criteria (Table 1). Licht et al.[2] compared hospitalized subjects participating in an RCT with those inpatients who did not qualify for the RCT. In contrast, Zarin et al.[3] examined subjects from a published report of an RCT of hospitalized adults with bipolar I disorder.[10] Patients of participating psychiatrists in the American Psychiatric Association's Practice Research Network were used as the comparison sample in this study.[3]

Given the importance of generalization of pharmacology study findings, it was deemed important to study this issue in children. It was elected to investigate this issue by comparing diagnostic and course features of the outpatient volunteers in a child bipolar I RCT to outpatient children with bipolar I disorder obtained by consecutive new case ascertainment from pediatric and child psychiatric sites. Specifically, the first 144 volunteers in the ongoing Treatment of Early Age Mania (TEAM) (NCT00057681) multisite RCT of pharmacotherapy for child bipolar I disorder, which began recruiting volunteers in 2003, were compared to outpatient participants in the Phenomenol-

Table 1. Studies of the Generalizability of Randomized Controlled Trials (RCTs) for Bipolar I Disorder

	RCT			Comparison Sample				
Source	N	Age (y)	Inpatient/ Outpatient	Description	N	Age (y)	Inpatient/ Outpatient	% Ineligible for RCT
Licht et al[2]	27	Median = 40	Inpatient	Patients excluded from RCT	137	Median = 43	Inpatient	83.5
Zarin et al[3]	179	Mean = 35.8[a]	Inpatient	Patients of participating APA PRN psychiatrists	92	Mean ± SD = 43.4 ± 1.6	NA	55.3
Tillman and Geller (present study)	144[b]	Mean ± SD = 10.4 ± 2.3[c]	Outpatient	Subjects obtained by consecutive new case ascertainment[d]	103	Mean ± SD = 10.9 ± 2.3[c]	Outpatient	7.8

[a]Standard deviation not given.
[b]The Treatment of Early Age Mania (TEAM)-RCT study is ongoing. N = 144 subjects recruited between March 25, 2003, and March 21, 2005.
[c]Overlapping age range of the TEAM-RCT and Phenomenology-Consecutive study samples was 7 to 15 years.
[d]Subjects were obtained by consecutive new case ascertainment from designated pediatric and child psychiatric facilities.
Abbreviations: APA PRN = American Psychiatric Association's Practice Research Network, NA = not available.

ogy and Course of Pediatric Bipolar Disorders study. The Phenomenology study was the first National Institute of Mental Health (NIMH)–funded study of the phenomenology and longitudinal course of child mania, and consecutive new case ascertainment took place from 1995 to 1998.

For clarity of reading, throughout the article, the Treatment of Early Age Mania (TEAM) RCT will be referred to as the TEAM-RCT study, and the Phenomenology study, which obtained subjects by consecutive new case ascertainment, will be referred to as the Phenomenology-Consecutive study.

METHOD

Recruitment for TEAM-RCT

Subjects in this communication from the ongoing TEAM-RCT study were outpatients recruited between March 25, 2003, and March 21, 2005, from multiple sites (see acknowledgment at end of article) for participation in a pharmacologic treatment study of child bipolar I disorder. Recruitment strategies included newspaper, radio, and television advertisements; brochures; community talks; school and daycare contacts; community physicians; and study site Web sites.

Consecutive New Case Ascertainment for the Phenomenology Study

The Phenomenology-Consecutive study consisted of 3 groups of subjects: bipolar I disorder, attention-deficit/hyperactivity disorder (ADHD), and healthy control. This communication reports on only the bipolar I subjects. Subjects in the bipolar I and ADHD groups were obtained by consecutive new case ascertainment from designated pediatric and psychiatric sites in the St. Louis, Mo., area from 1995 to 1998. Details of subject ascertainment in the Phenomenology-Consecutive study have been previously published.[11,12] In brief, in the consecutive new case ascertainment schema, new cases at the designated, academically affiliated pediatric and psychiatric sites were screened according to an algorithm. This included every new case, even those who presented with sore throats and other nonpsychiatric symptoms. Thus, there was no bias to the selection of cases. Outpatient sites were used because planned inpatient ascertainment venues in St. Louis closed prior to subject enrollment in the study.

Study research nurses reviewed records from every new case at the psychiatric and pediatric facilities. All subjects without obvious exclusions were telephoned, and those still eligible after the telephone contact were given the baseline assessment by blinded, experienced research clinicians, who were different from the nurses who initially reviewed the records. These research clinicians were blinded to the diagnostic status of the subjects. Blinding was possible because subjects with bipolar disorder were randomly mixed in with subjects from 2 control groups.[11] Of the 1468 new cases at the planned ascertainment venues, 308 were not excluded after the initial telephone contact and were scheduled for in-person baseline assessment. Of these cases, 92 fit the conservative bipolar I disorder criteria (i.e., Phenomenology-Consecutive subjects were required to have elation and/or grandiosity [i.e., cardinal symptoms] and a Children's Global Assessment Scale [CGAS][13,14] score ≤ 60), and 81 subjects with ADHD met criteria for the ADHD group.[11] The 6.3% rate of bipolar I disorder in this clinical population is consistent with a recent epidemiologic study that reported a 5.0% prevalence of bipolar I disorder among 12- to 29-year-olds.[15]

The healthy control group was obtained by a random survey that matched healthy subjects to bipolar I subjects by age, sex, socioeconomic status, ethnicity, and zip code.[11]

Study Inclusion and Exclusion Criteria

Because TEAM-RCT subjects were aged 6 to 15 years and Phenomenology-Consecutive subjects were aged 7 to 16 years, only subjects in the overlapping age group of 7 to 15 years were analyzed for this communication.

Inclusion criteria common to the TEAM-RCT study and the bipolar I subjects in the Phenomenology-Consecutive study were age of 7 to 15 years, good physi-

cal health, and current DSM-IV bipolar I disorder (manic or mixed phase). Subjects could be either male or female. A CGAS score ≤ 60 was needed to establish significant clinical impairment.[13,14]

Exclusion criteria common to both studies were IQ < 70, pervasive developmental disorders, schizophrenia, epilepsy or other major medical or neurologic disorder, baseline substance dependency or pregnancy, and mania only while taking antidepressant or stimulant medication. There were no family history exclusions in either study.

An additional inclusion criterion for the bipolar I subjects in the Phenomenology-Consecutive study was that the phenotype was defined by having at least 1 of the 2 cardinal symptoms of mania (i.e., elation and/or grandiosity). Of note, although this cardinal symptom criterion was not a requirement in the ongoing TEAM-RCT study, all subjects in the TEAM-RCT study also had elation and/or grandiosity at baseline (see Table 3).

An exclusion criterion specific to the Phenomenology-Consecutive study was adopted status, due to concurrent family and genetic studies.[16,17] In the TEAM-RCT study, sexually active females not using a pill, intrauterine device, or barrier method of contraception; nursing females; and subjects requiring inpatient care at baseline were excluded. An additional exclusion criterion for the TEAM-RCT study was that subjects could not have a treatment history including more than 1 of the 3 study medications.

The rationales for the inclusion and exclusion criteria included the following. Subjects in the Phenomenology-Consecutive study needed to be in a current manic episode because the study assessed phenomenology of child mania, and subjects in the TEAM-RCT study needed to be in a current manic episode because the study was a treatment study of child mania. Conservative diagnostic criteria for child mania were chosen to address controversies in the field.[17–20] Bipolar I subjects in the Phenomenology-Consecutive study were required to have at least 1 of the cardinal symptoms of mania (i.e., elation and/or grandiosity) to avoid diagnosing mania only by symptoms that overlapped with those for ADHD (i.e., distractibility, hyperactivity).[11,21] Subjects in either study could not have baseline pregnancy or substance dependency, to keep from confounding the mental status through gestational hormonal changes[22] or illicit drug use. Sexually active females not using contraception were excluded from the TEAM-RCT study for safety of the fetus, and nursing females were excluded because the study medications may cross into the infant. However, since the mean age of subjects in the TEAM-RCT study was 10.9 years (with a narrow standard deviation), the exclusion of sexually active females not using contraception was unlikely to affect the sample. Adoption was an exclusion criterion in the Phenomenology-Consecutive study, due to concurrent family and genetic studies.[16] Subjects in the TEAM-RCT study could not have a treatment history including more than 1 of the 3 study medications because subjects needed to be randomly assigned to a drug they had not previously been treated with.

Assessment

The Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS)[23,24] was the main diagnostic tool in both the TEAM-RCT and Phenomenology-Consecutive studies. The WASH-U-KSADS is a semistructured interview that includes expanded items to assess prepubertal mania, cycling patterns (e.g., ultradian, ultrarapid), current and lifetime episodes, onsets and offsets of each symptom and syndrome, and ADHD and other DSM-IV diagnoses. The narrative accompanying each WASH-U-KSADS item needed to justify the rating with respect to onset, offset, frequency, duration, severity, and specific examples. On the WASH-U-KSADS, item ratings of ≥ 4 indicate definite clinical impairment and count toward DSM-IV diagnoses. Examples of prepubertal manifestations of mania have been previously published.[21] The WASH-U-KSADS has been shown to have excellent reliability (κ values of 0.82–1.00).[24] Experienced research clinicians with established interrater reliability administered the WASH-U-KSADS separately to parents about their children and to children about themselves.[24,25] Parent and child responses were combined following the method of Bird et al.[26] In this schema, the most severe rating for a WASH-U-KSADS item from either the parent or child interview determined the severity for that item.

The CGAS[13,14] is a global severity measure. The clinicians who administered the WASH-U-KSADS derived CGAS scores based on subjects' intensity of symptoms and impaired functioning in social, family, school, and work settings. Socioeconomic status was determined by the Hollingshead Four Factor Index of Social Status,[27] and pubertal status was determined by the Pubertal Status Questionnaire in subjects at least 10 years of age.[28]

Consensus conferences were held with a child psychiatrist and the research nurses who administered the instruments in order to confirm diagnoses.[29–31] In these meetings, materials including assessment instruments, school reports, agency records, pediatrician charts, videotapes of WASH-U-KSADS interview sessions with parents, and videotapes of WASH-U-KSADS interview sessions with children were reviewed.

Reliability of Assessments

In the TEAM-RCT study, research clinicians who conducted the subject interviews were trained at Washington University in St. Louis, where they gained interrater reliability with Washington University in St. Louis raters. Interrater reliability for the RCT was 90% agree-

ment on DSM-IV diagnoses and mania criteria. Across-site reliability was accomplished throughout the TEAM-RCT study using the following method. Videotapes of all interviews of parents about their children and of children about themselves from the TEAM-RCT sites were rated by the Washington University research clinicians. Real-time feedback was used to resolve any discrepancies.

In the Phenomenology-Consecutive study, as detailed in Geller et al.,[24] the research clinicians who administered the WASH-U-KSADS were trained to interrater reliability and recalibrated annually. Interrater reliability was achieved when raters reached 100% agreement on DSM-IV diagnoses and individual criteria 5 consecutive times as observer and interviewer.

Depression, Rapid Cycling, Psychosis, and Suicidality

Depression was defined as DSM-IV major depressive disorder, minor depressive disorder, or dysthymia occurring any time prior to or at the baseline assessment.

There has been confusion in the field of child bipolar disorder over definitions of rapid cycling and episodes. For this reason, Tillman and Geller[32] proposed the following definitions based on definitions from Kramlinger and Post.[33] Current episode refers to the time from onset of the current mania diagnosis to the baseline assessment, and cycles refer to mood switches during the current episode. In this schema, ultradian cycling comprises mood switches occurring multiple times a day, every or almost every day, during the current episode. Ultrarapid cycling comprises mood switches occurring every few days during the current episode.[32] For example, an 8-year-old boy had multiple daily cycles (from "high over the charts" to the depths of despair) every day for 2 years. He would be said to have an episode lasting 2 years, characterized by ultradian cycling.

Psychosis was defined as clinically impairing, malignant, pathologic hallucinations and delusions that did not only occur hypnagogically or hypnopompically. Following this definition, a subject hearing an occasional voice call his or her name would not be considered psychotic, while a subject hearing a voice instructing him or her to commit suicide would be considered psychotic.

Suicidality was assessed with the WASH-U-KSADS items on suicidal ideation and behavior.

Statistical Analyses

Demographic and severity characteristics in the 2 study groups were compared using 2-tailed t tests for continuous variables (age, age at mania onset, duration of current mania episode, and CGAS score) and χ^2 tests for categorical variables (sex, pubertal status, race, and socioeconomic status).

Prevalence of mania items and characteristics in the 2 study groups were compared using logistic regression, controlling for sex and age at onset of current mania episode. These variables were controlled for because the Phenomenology-Consecutive sample was significantly more often male and had a significantly older age at onset of current episode. Logistic regression analysis could not be performed when either all of the subjects or none of the subjects in a group had the item or characteristic being compared.

Differences in mania symptoms and characteristics were previously examined in the Phenomenology-Consecutive study by subject recruitment site (pediatric vs. psychiatric).[12] Since several symptoms and characteristics were found to be more prevalent in subjects obtained at psychiatric sites, data from the TEAM-RCT and Phenomenology-Consecutive samples were reanalyzed, using only the subjects in the Phenomenology-Consecutive study obtained at pediatric facilities (N = 37).

Significance levels were determined using the Bonferroni method of correcting for multiple comparisons. Using this method, the overall significance level ($p < .05$) was divided by the number of comparisons made. This resulted in Bonferroni-corrected significance levels of $p < .003$ for the mania items in Table 3 and $p < .006$ for the mania characteristics in Table 4.

RESULTS

There were 144 subjects from the ongoing TEAM-RCT study in the overlapping age range of 7 to 15 years. There were 103 Phenomenology-Consecutive subjects with bipolar I disorder in the age range of 7 to 15 years, which included 87 from the bipolar I group and 16 who entered the Phenomenology-Consecutive study in the ADHD group but later developed bipolar I disorder (manic or mixed phase). For baseline ADHD subjects who switched to bipolar I disorder during follow-up, data from the assessment at which bipolar I disorder was first present were used for this analysis.

Demographic Characteristics

Demographic characteristics are shown in Table 2. Phenomenology-Consecutive subjects were significantly more often male than TEAM-RCT subjects (68.0% vs. 52.1%; $\chi^2 = 6.2$, $p = .013$).

Mania Symptoms

A comparison of mania symptoms in the TEAM-RCT and Phenomenology-Consecutive samples is shown in Table 3, where it can be seen that certain mania symptoms had a significantly higher prevalence in the TEAM-RCT sample.

Illness Severity and Course Characteristics

TEAM-RCT subjects had a significantly younger age at onset of current episode (5.6 ± 2.8 vs. 7.7 ± 3.2 years; $t = 5.4$, $df = 245$, $p < .0001$) and longer duration of current

Table 2. Comparison of Demographic Characteristics in the TEAM-RCT and Phenomenology-Consecutive Studies

	Total (N = 247)		TEAM-RCT (N = 144)		Phenomenology-Consecutive (N = 103)		TEAM-RCT vs Phenomenology-Consecutive	
Characteristic	Mean	SD	Mean	SD	Mean	SD	t	p
Age at baseline, y	10.6	2.3	10.4	2.3	10.9	2.3	1.8	NS
	%	N	%	N	%	N	χ^2	p
Sex								
Male	58.7	145	52.1	75	68.0	70	6.2	.013
Female	41.3	102	47.9	69	32.0	33		
Pubertal status								
Prepubertal	58.3	144	59.7	86	56.3	58	0.3	NS
Pubertal	41.7	103	40.3	58	43.7	45		
Race								
White	84.2	208	81.9	118	87.4	90	1.3	NS
Other	15.8	39	18.1	26	12.6	13		
Socioeconomic status								
Class I (highest class)	25.9	64	22.2	32	31.1	32	3.8	NS
Class II	42.9	106	43.1	62	42.7	44		
Class III	21.9	54	23.6	34	19.4	20		
Class IV	7.3	18	8.3	12	5.8	6		
Class V (lowest class)	2.0	5	2.8	4	1.0	1		

Abbreviations: Phenomenology-Consecutive = Phenomenology and Course of Pediatric Bipolar Disorders study, TEAM-RCT = Treatment of Early Age Mania randomized controlled trial.

Table 3. Comparison of Mania Symptoms in the TEAM-RCT and Phenomenology-Consecutive Studies

	Total (N = 247)		TEAM-RCT (N = 144)		Phenomenology-Consecutive (N = 103)		TEAM-RCT vs Phenomenology-Consecutive	
Mania Symptom	%	N	%	N	%	N	χ^2	p[a]
Elated mood/grandiosity	100.0	247	100.0	144	100.0	103	…	…
Elated mood	95.1	235	97.2	140	92.2	95	0.9	NS
Grandiosity	91.9	227	95.1	137	87.4	90	4.0	NS
Flight of ideas/racing thoughts	83.4	206	95.1	137	67.0	69	20.5	< .0001
Flight of ideas	74.5	184	90.3	130	52.4	54	30.5	< .0001
Racing thoughts	61.9	153	72.9	105	46.6	48	10.8	.001
Decreased need for sleep	59.9	148	78.5	113	34.0	35	37.1	< .0001
Poor judgment	94.7	234	98.6	142	89.3	92	7.3	NS
Hypersexuality	55.5	137	66.7	96	39.8	41	17.1	< .0001
Daredevil acts	78.1	193	89.6	129	62.1	64	19.7	< .0001
Silliness/laughing	82.2	203	91.0	131	69.9	72	18.6	< .0001
Uninhibited people-seeking	66.0	163	71.5	103	58.3	60	4.8	NS
Irritable mood	98.0	242	100.0	144	95.1	98	…	…
Accelerated speech	97.6	241	99.3	143	95.1	98	1.7	NS
Distractibility	97.2	240	98.6	142	95.1	98	2.2	NS
Increased energy	100.0	247	100.0	144	100.0	103	…	…
Hyperenergetic	93.9	232	95.1	137	92.2	95	0.0	NS
Increased productivity	48.2	119	61.8	89	29.1	30	19.1	< .0001
Sharpened thinking	52.2	129	61.1	88	39.8	41	4.2	NS
Increased goal-directed activity	55.9	138	67.4	97	39.8	41	8.7	.003

[a]Bonferroni-corrected level of significance was p < .003.
Abbreviations: Phenomenology-Consecutive = Phenomenology and Course of Pediatric Bipolar Disorders study, TEAM-RCT = Treatment of Early Age Mania randomized controlled trial.

mania episode (4.8 ± 2.4 vs. 3.2 ± 2.3 years; t = 5.2, df = 245, p < .0001) than Phenomenology-Consecutive subjects (Table 4). CGAS scores were significantly lower in the TEAM-RCT sample compared to the Phenomenology-Consecutive sample (38.7 ± 6.7 vs. 43.7 ± 7.6; t = 5.5, df = 245, p < .0001).

A comparison of course characteristics in the TEAM-RCT and Phenomenology-Consecutive samples is also shown in Table 4. TEAM-RCT subjects had a significantly higher prevalence of psychosis, ultradian cycling, and suicidality than subjects in the Phenomenology-Consecutive study.

Fit of Phenomenology-Consecutive Subjects to TEAM-RCT Study Criteria

All subjects in the Phenomenology-Consecutive study met the diagnostic inclusion requirements for the TEAM-RCT study. However, 7.8% (N = 8) of the Phenomenology-Consecutive subjects would not have been eligible for the TEAM-RCT study, due to the exclusion criterion of having

Table 4. Comparison of Course Features in the Team-RCT and Phenomenology-Consecutive Studies

	Total (N = 247)		TEAM-RCT (N = 144)		Phenomenology-Consecutive (N = 103)		TEAM-RCT vs Phenomenology-Consecutive	
Course Feature	Mean	SD	Mean	SD	Mean	SD	t	p[a]
Age at onset of current episode, y	6.5	3.2	5.6	2.8	7.7	3.2	5.4	< .0001
Duration of current episode, y	4.1	2.5	4.8	2.4	3.2	2.3	5.2	< .0001
CGAS score	40.7	7.5	38.7	6.7	43.7	7.6	5.5	< .0001
	%	N	%	N	%	N	χ^2	p
Depression, lifetime	87.0	215	86.1	124	88.3	91	0.2	NS
Multiple episodes per year	0.0	0	0.0	0	0.0	0	…	…
Ultrarapid cycling during episode	3.6	9	1.4	2	6.8	7	1.6	NS
Ultradian cycling during episode	90.3	223	98.6	142	78.6	81	12.0	.001
Psychosis	74.5	184	84.0	121	61.2	63	11.9	.001
Suicidality	46.6	115	61.1	88	26.2	27	27.0	< .0001

[a]Bonferroni-corrected level of significance was p < .006.
Abbreviations: CGAS = Children's Global Assessment Scale, Phenomenology-Consecutive = Phenomenology and Course of Pediatric Bipolar Disorders study, TEAM-RCT = Treatment of Early Age Mania randomized controlled trial.

been treated with 2 or more of the TEAM-RCT study medications.

Prior Antimanic Medication Use

At baseline, 76.4% of TEAM-RCT subjects and 65.0% of Phenomenology-Consecutive subjects had never been treated with an antimanic drug. Stated alternatively, only 23.6% and 35.0% of subjects in the TEAM-RCT and Phenomenology-Consecutive studies had been treated with a mood stabilizer. The rates were not significantly different between study groups ($\chi^2 = 0.9$, df = 1, p = .355).

TEAM-RCT Versus Phenomenology-Consecutive Subjects From Pediatric Sites

Of the 103 Phenomenology-Consecutive subjects, 37 were obtained at pediatric sites. Comparisons of demographic variables, mania symptoms, and mania characteristics between the TEAM-RCT sample and these 37 Phenomenology-Consecutive subjects were the same as the results presented above, with the following exceptions. The 37 Phenomenology-Consecutive subjects obtained at pediatric sites were significantly older than the TEAM-RCT subjects at baseline (11.3 ± 2.2 vs. 10.4 ± 2.3 years; t = 2.2, p = .03). In addition, rates of racing thoughts, inappropriate laughing, and psychosis were not significantly different in the TEAM-RCT and Phenomenology-Consecutive samples when only the 37 Phenomenology-Consecutive subjects obtained at pediatric sites were considered, possibly due to small sample size.

DISCUSSION

Overall, there were statistically significant differences in prevalence of mania symptoms and course features between the TEAM-RCT and Phenomenology-Consecutive samples. Higher prevalences of psychosis, ultradian cycling, and suicidality and lower CGAS scores are consistent with greater severity in the TEAM-RCT sample. Because subjects in both studies were severely ill, however, these differences may not be clinically meaningful. For example, a CGAS score of 39 compared to a CGAS score of 44 or a mean duration of current mania episode of 4.8 years compared to a duration of 3.2 years are all consistent with high severity and chronicity. Both groups had a chronic, severe illness. This chronic presentation has been found in 2 large NIMH-funded studies of child bipolar disorder[19,34] and has been reported in multiple retrospective analyses.[35–39] Thus, long current episode duration appears to be a consistent characteristic of childhood bipolar I disorder.

Of note, the mania symptom of decreased need for sleep was significantly more prevalent in the TEAM-RCT sample (78.5%) than in the Phenomenology-Consecutive sample (34.0%). The rate of decreased need for sleep observed in the TEAM-RCT sample is more consistent with other reports of child mania symptoms that found rates of decreased need for sleep of 61.1% to 95.1%.[40] To our knowledge, however, the Phenomenology-Consecutive study is the only study of child bipolar I disorder in which consecutive new case ascertainment was used, so it is possible that the higher rates of decreased need for sleep found in other samples may be due to the ascertainment schema. Convenience samples, including the TEAM-RCT sample, appear to be more likely to have severe symptomatology, including decreased need for sleep.

One question that might arise is whether comparisons of the TEAM-RCT sample to the Phenomenology-Consecutive subjects obtained at pediatric sites are similar to comparisons of the TEAM-RCT sample to the entire Phenomenology-Consecutive sample (obtained at both pediatric and psychiatric sites). Analyses (data not shown) found that comparisons to the subjects obtained at pediatric sites were similar to those of the whole Phenomenology-Consecutive group. This would be ex-

pected, because a detailed comparison of pediatric versus psychiatric setting subjects in the Phenomenology-Consecutive study[12] showed that subjects from both pediatric and psychiatric facilities were severely ill.

Although baseline age did not differ between the TEAM-RCT and Phenomenology-Consecutive samples, TEAM-RCT subjects had a significantly younger age at onset of current mania episode (5.6 ± 2.8 vs. 7.7 ± 3.2 years). However, it is not clear that this significant, but relatively small, difference in age at onset would have clinical meaning. To examine this issue, the TEAM-RCT and Phenomenology-Consecutive data were analyzed for only subjects matched by age at onset. These results (data not shown) did not differ from the results of the analysis that used the total 247 subjects. Thus, age at onset did not determine the severity of illness in the TEAM-RCT sample.

Support for the generalizability of the TEAM-RCT sample is illustrated by the finding that only 7.8% of the Phenomenology-Consecutive sample would not have fit the TEAM-RCT study criteria. Alternatively stated, 92.2% of the Phenomenology-Consecutive sample would have qualified for the TEAM-RCT study. The sole reason for these Phenomenology-Consecutive subjects' not meeting the TEAM-RCT criteria was prior use of TEAM-RCT study medications. Specifically, subjects were excluded from the TEAM-RCT study if they had a lifetime history of receiving any 2 of the 3 TEAM-RCT study medications. This low rate of 7.8% of a clinical sample not fitting an RCT differs from rates in adult studies that examined the representativeness of RCTs in adult bipolar disorder. In the adult investigations, 55.3%[3] to 83.5%[2] of clinical subjects were excluded from the RCTs. Speculations on the reasons for high generalization of the child RCT compared to the lower generalization reported in the 2 adult studies include that both adult RCTs were of hospitalized inpatients and that adults may have had more exclusions for complicated treatment history, major medical illness, substance abuse, and pregnancy.

Generalization of the TEAM-RCT subjects to those seen in academic clinical centers was supported, because only 7.8% of Phenomenology-Consecutive subjects would not have qualified for the TEAM-RCT study. However, because the TEAM-RCT subjects were more severely ill than the Phenomenology-Consecutive subjects (i.e., significantly higher prevalences of psychosis, ultradian cycling, and suicidality, and lower CGAS scores in the TEAM-RCT sample), it is unclear if treatment findings from the TEAM-RCT will be applicable to children with less severe mania. Moreover, although the great majority of clinical bipolar I cases may qualify for child bipolar I RCTs, it is possible that only the most severely ill cases may seek participation in pharmacotherapy trials.

The intent of this communication is not to argue that convenience samples can replace samples obtained by consecutive new case ascertainment for studies of child bipolar I disorder. Rather, convenience samples for child bipolar I RCTs may be more representative of clinical child bipolar I disorder in contrast to the lack of representativeness of adult bipolar I RCTs to adult bipolar I disorder.

Limitations

One limitation is that the median socioeconomic status for both study samples was in the second highest of 5 classes. At the time of subject ascertainment for the Phenomenology-Consecutive study, there was no facility or private practice in the area available to obtain subjects by consecutive new case ascertainment from lower socioeconomic backgrounds. Because consecutive new case ascertainment requires that the physician send letters to each new case in their practice, it is understandable that not all practices agree to do this.

The reason for the high socioeconomic status in the TEAM-RCT study is not clear, as efforts were made to recruit across the socioeconomic domain. Therefore, the results reported in this communication may not generalize to lower socioeconomic status settings.

Another limitation is that all subjects in the TEAM-RCT and Phenomenology-Consecutive studies were outpatients. In the Phenomenology-Consecutive study, planned inpatient ascertainment sites closed prior to the start of the study. The TEAM-RCT study was designed to include only outpatients, to mimic real world practice. Thus, findings may not generalize to inpatient populations.

The Phenomenology-Consecutive study bipolar I phenotype required elation and/or grandiosity as one criterion. Therefore, findings presented in this communication may not generalize to other child bipolar I phenotypes. However, elation and grandiosity were not requirements for the TEAM-RCT sample. Nevertheless, all TEAM-RCT subjects had elation and/or grandiosity.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Melissa P. DelBello, M.D., at delbelmp@email.uc.edu.

