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Clinical course of children with a depressive spectrum disorder and transient manic symptoms

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Abstract

Objective—To assess rates of conversion to bipolar spectrum disorder (BPSD) and risk factors associated with conversion in children with depressive spectrum disorders (DSD) and transient manic symptoms (TMS) over 18 months. TMS are manic-like symptoms of insufficient duration or number to warrant a diagnosis of BPSD.

Methods—Participants were 165 children (mean = 9.9 years, SD = 1.3) with mood disorders from the Multi-Family Psychoeducational Psychotherapy (MF-PEP) treatment study; 37 with DSD+TMS, 13 with DSD, and 115 with BPSD. All were assessed with standardized instruments on four occasions over 18-months, with half receiving MF-PEP after their baseline assessment and half receiving MF-PEP after a one-year wait-list condition.

Results—At baseline, the Children's Global Assessment Scale scores did not differ significantly between the DSD+TMS, DSD, and BPSD groups. Conversion rates to BPSD were significantly higher for the DSD+TMS group (48.0%) compared to the DSD group (12.5%). Conversion was significantly more frequent for participants in the one-year wait-list control group (60%) compared to the immediate treatment group (16%). Clinical presentation, family environment, and family history did not differ significantly between the small subset of DSD+TMS participants who did convert to BPSD at follow-up and those who did not convert. Baseline functional impairment was greater for the converted group than the non-converted group.

Conclusions—Transient manic symptoms are a risk factor for eventual conversion to BPSD; psychoeducational psychotherapy may be protective. As this exploratory study had a small sample size and did not correct for multiple comparisons, additional studies with larger sample sizes are needed.

Keywords

aggression conversion; bipolar disorder; children; clinical course; depression; irritability; mania

Introduction

Relatively little is known about the longitudinal course of bipolar disorder in children (1). Some adult mood researchers (2,3) hypothesize that unipolar depression and bipolar disorder [mainly bipolar II disorder (BP-II)] lie on a dimensional continuum, as they share several

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common features (age at onset, atypical depressive features, depressive mixed state, number of recurrences, and genetic vulnerability).

Even less is known about the full spectrum of bipolar disorder in children [bipolar spectrum disorders (BPSD): bipolar I disorder (BP-I), BP-II, cyclothymia, and bipolar disorder not otherwise specified (BP-NOS)]. Only one longitudinal study, the *Course and Outcome of Bipolar Youth (COBY)* has examined manic symptoms in children diagnosed with BPSD (4–6). No studies to date have longitudinally assessed the clinical importance of transient manic symptoms (TMS) in children with depressive spectrum disorders [DSD: major depressive disorder (MDD) and/or dysthymic disorder (DD)] to determine whether these transient subthreshold manifestations later progress to a recognized BPSD. TMS are defined, for the purposes of this study, as manic-like symptoms of insufficient duration or number to warrant a diagnosis of BPSD, including standardized criteria for BP-NOS, similar to those used in the COBY study (5). Table 1 provides TMS diagnostic criteria. Two case presentations (using pseudonyms) below illustrate how TMS presented in this study.

Case study: 8-year-old girl

At baseline, Jane was diagnosed with attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, separation anxiety disorder, and MDD+TMS. She recalled feeling intensely irritable several times in the previous two weeks without any trigger; the longest period lasted 30 minutes and she indicated that this was “the maddest” she had ever been. During these brief periods of intense irritability, she hit and bit other people. In addition, Jane’s mother reported brief periods wherein she seemed “too high for no apparent reason.” These lasted 1–2 hours/day for a few consecutive days. While in this “high” mood, Jane rapidly switched from topic to topic in conversation, and was caught grabbing her brother’s penis, and watching adult-rated sex scenes on DVDs in the family home. She was also “obsessed with her own breast development.” Jane converted to BP-I, most recent episode depressed at the six-month follow-up.

In this case example, Jane was noted to experience intense, but brief periods of irritability and elated mood, with accompanying racing thoughts and excessive involvement in pleasurable activities with high potential for painful consequences. However, their frequency and duration were brief, despite resulting in impairment, such that Jane did not meet criteria for BP-I, BP-II, BP-NOS, or cyclothymia.

Case study: 11-year-old boy

John was diagnosed at baseline with dysthymic disorder + TMS, ADHD, and conduct disorder. His grandmother and legal guardian, described periods in the past when John had devoted himself to unrealistic (and unsuccessful) goals, such as taking apart bicycles and fixing them as training to operate a bicycle repair business, or believing he was so strong that he could “beat up Arnold Schwarzenegger.” However, those were relatively fleeting occurrences and did not correspond with other symptoms of mania. In the week prior to the assessment, John reported having one day when he talked too fast and couldn’t be interrupted, but had no other accompanying manic symptoms. He also reported occasional nights where he didn’t feel he needed much sleep. John converted to BP-II at the 12-month follow-up.

In this case example, John had several isolated but vivid reports of grandiosity, decreased need for sleep, and pressured speech, but they were not of the frequency or duration nor were they accompanied by sufficient other manic symptoms that clustered during a unified time period to warrant a bipolar spectrum diagnosis.

Retrospective adult studies indicate that bipolar disorder with a prepubertal or adolescent onset is common among those diagnosed with this disorder and earlier age of onset is associated with a more pernicious course (7–9). A majority of the respondents in these studies experienced impairing symptoms prior to receiving a bipolar disorder diagnosis. In one study, nearly three-quarters of participants reported experiencing one or more impairing manic symptom while diagnosed with unipolar depression (7). This can pose a problem, as treatment with antidepressants may trigger mania (10). Even though manic symptoms often manifest at a younger age, accurate diagnosis and treatment may be delayed by the clinician's failure to consider such a diagnosis (8).

Rates of conversion from unipolar depressive disorder to subsequent bipolar disorder in adults have ranged from 12.5% in an outpatient sample followed for 11 years (11) to 45–50% for an inpatient sample followed for 15 to 23 years (12,13). Clinical features associated with conversion include depression with psychotic features, a history of more than six depressive episodes, and a positive family history of mania.

Several prospective studies have assessed the rate and predictors of conversion to bipolarity in children and adolescents diagnosed with MDD (14,15). Others have prospectively assessed adults with bipolar disorder who had prepubertal MDD (16). These studies have found that conversion from MDD to BP-I and BP-II in prepubertal children and adolescents is relatively common, ranging from 20–49%, depending on the length of follow-up. Thus, diagnostic stability appears low for childhood-onset MDD (17). Family history of bipolar disorder, rapid symptom onset, psychomotor retardation, mood congruent psychosis, and pharmacologically induced mania all have been identified as predictors of conversion. These studies have important clinical implications. First, children with MDD and their families should be alerted to the possibility of developing bipolar disorder and taught to recognize prodromal symptoms associated with mania (18). Second, clinicians should be aware that children with MDD are at high risk for converting to bipolar disorder and should monitor them for emergent prodromal symptoms. Third, due to high rates of conversion, significant caution should be taken when prescribing antidepressants to children with MDD, as antidepressants may trigger childhood mania (10). Finally, research to aid in predicting which children will convert to bipolar disorder after their index MDD episode is of vital importance to clinicians (11).

Some studies have assessed prodromal symptoms and risk factors for childhood-onset bipolar disorder in high-risk youth (19,20). Familial high-risk youth do not show classic symptoms of mania; instead, they show increased severity of depressed and irritable mood and problems with mood regulation. Very little is known about bipolar prodromes in young children.

No studies have assessed the rates of conversion to BPSD in children with DSD+TMS. Also, no studies to date have examined the influence of psychosocial treatments on subsequent conversion to BPSD. Studying rates of conversion from DSD to BPSD allows for the assessment of risk factors that can predict bipolarity. Thus, the aims of the present study were to determine rates of, and risk factors for, conversion in children with DSD +TMS over an 18-month follow-up period. The following hypotheses were employed:

Hypothesis 1: At baseline, children with DSD+TMS will have lower Children's Global Assessment Scale (C-GAS) scores than children with DSD, but higher scores than children with BPSD.

Hypothesis 2: Children with DSD+TMS at baseline will convert to BPSD at follow-up at a higher rate than children with only DSD at baseline.

Hypothesis 3: Conversion rates will not differ as a result of participation in psychoeducational psychotherapy.

Hypothesis 4: Children with DSD+TMS at baseline who convert to BPSD at follow-up (converted group) will demonstrate greater impairment than those who do not convert (i.e., non-converted group) on the following baseline composite variables: clinical presentation, family environment, and family history.

Composite variables were used to reduce the number of analyses conducted in testing primary hypotheses. Secondary hypotheses were conducted to see which, if any, components of composite variables differed (*clinical presentation*: greater severity of prodromal manic symptoms, longer duration of prodromes, lower C-GAS scores; *family environment*: greater number of life events, more critical and hostile family environment; *family history*: higher rates of bipolar disorder diagnosis and symptoms for parents and second-degree relatives, higher rates of a loaded family history, and higher mood severity in the parent).

Methods

Participants

A total of 165 prepubertal children (ages 8–11 at baseline; mean = 9.9 years, SD = 1.3) with a mood diagnosis participated in the Multi-Family Psychoeducational Psychotherapy (MF-PEP) treatment study. The mood disorder diagnoses eligible for this study included MDD, DD, BP-I, BP-II, and BP-NOS. One or two parents/caregiver informants (hereafter referred to as parents) also participated. Four assessments were completed over an 18-month period (*Time 1*: baseline; *Time 2*: 6 months; *Time 3*: 12 months; *Time 4*: 18 months).

Approximately one-half of the sample ($n = 78$) received immediate treatment (IMM); the remaining participants ($n = 87$) were in a one-year wait-list control (WLC) condition and received treatment after their Time 3 assessment. Results of the MF-PEP are reported elsewhere (21,22).

At baseline, 37 participants were in the DSD+TMS group, 13 in the DSD group, and 115 in the BPSD group (see Figure 1). The three groups did not differ significantly on any baseline demographic characteristics although age and intelligence quotient (IQ) marginally differed between the groups (see Table 2). Due to the dropouts at Time 3 and Time 4, Hypothesis 2 compared 25 DSD+TMS participants with 8 DSD participants, while Hypothesis 3 compared 12 immediate treatment DSD+TMS participants with 15 wait-list control DSD +TMS participants. The subsample (DSD+TMS and DSD groups) did not significantly differ on age and IQ ($p = 0.36, 0.60$, respectively). Hypothesis 4 and the supplementary analyses compared 12 participants from the converted group (participants with DSD+TMS at Time 1 who converted to BPSD at follow-up) to 13 participants from the non-converted group (participants with DSD+TMS at Time 1 who did not convert to BPSD at follow-up). Hypotheses 2, 3 and 4 were repeated using intent-to-treat (ITT) analyses. Twelve participants had their last observation carried forward to impute Time 4 missing data, which resulted in 37 participants for the DSD+TMS group (12 converters, 25 non-converters) and 13 for the DSD group (1 converter, 12 non-converters).

Procedure

Study procedures were approved by the Ohio State University Institutional Review Board for Human Subjects (Columbus, OH, USA). After their baseline assessment, children were randomized into the IMM group or WLC condition. The IMM group participated in MF-PEP between their Time 1 and Time 2 assessments. The WLC group participated in MF-PEP between their Time 3 and Time 4 assessments. All were encouraged to continue

treatment-as-usual (medication, psychosocial, and school-based interventions) throughout the study duration.

Family intervention

MF-PEP is comprised of eight weekly 90-minute group therapy sessions for parents and children emphasizing psychoeducation, social support, and skills development based on cognitive-behavioral and family systems interventions. Detailed descriptions of session content and treatment outcome appear elsewhere (22,23).

Instruments

Sociodemographic information, including age, sex, race, income level, family structure, and the parent's relationship with the child (e.g., biological parent, stepparent, adoptive parent) was collected at baseline. Instruments used in this study are described below.

A diagnostic interview, the Children's Interview for Psychiatric Syndromes–Child (ChIPS) (24) and Children's Interview for Psychiatric Syndromes–Parent (P-ChIPS) (25), was conducted at Time 1 and Time 3 to determine the child's diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (26). Severity of mood symptoms was assessed at each time period using the Mania Rating Scale (MRS) (27) and the Children's Depression Rating Scale–Revised (CDRS-R) (28).

A cognitive screen [Kaufman Brief Intelligence Test, Second Edition (29)] was administered at baseline to estimate cognitive ability and to rule out subjects with a full-scale IQ score of ≤ 70 .

Interviewers

Interviewers were doctoral students in clinical child psychology and the postdoctoral study coordinator. An extensive, standardized training procedure was employed prior to any staff conducting study assessments. This included didactics followed by mock ratings, and videotaped and live interviews. After establishing reliability ($\kappa \geq 0.70$) at each step, interviewers were videotaped performing live interviews, which were coded by the postdoctoral project coordinator. After reliability ($\kappa \geq 0.70$) was reached, interviewers conducted independent interviews. The project coordinator rated videotapes of 10% of the interviews; if interviewer 'drift' was detected, interviewers repeated training procedures until reliability was reestablished.

Follow-up interviews were conducted by graduate students as the study coordinator was no longer blinded to treatment status after baseline. Inter-rater reliability for all instruments was significant ($\kappa_{\text{SChIPS}} = 0.82$; $\kappa_{\text{SP-ChIPS}} = 0.78$).

Consensus conference

Within 24 hours of the assessment, interviewers and the principal investigator met to review study eligibility and diagnostic category (i.e., bipolar spectrum or depressive spectrum). Then, reports were prepared that included detailed descriptions of all mood symptoms, including severity and time course. These reports were reviewed independently by the principal investigator and a clinical child psychologist who specialized in childhood mood disorders. Subsequently, they completed a consensus conference rating that determined the specific diagnosis assigned (e.g., dysthmic disorder with or without TMS).

Clinical presentation

The C-GAS was completed after each assessment to document severity of impairment (30). Two clinical psychologists experienced in childhood mood disorders separately read reports that summarized each assessment, independently rated the C-GAS, and then held a consensus conference at which a final C-GAS score was determined. Inter-rater reliability (score $\pm$ 5) was good ($kappa = 0.68$, 95% confidence interval: 0.59, 0.78).

To calculate *prodrome duration*, age of onset for prodromal symptoms was recorded in years and months. Prodromal symptoms were defined as manic or depressive symptoms that interfered with functioning but did not meet diagnostic criteria for a specific mood disorder. When prodromal symptoms were absent, duration was coded as zero. Prodrome duration was calculated by subtracting age of onset for prodromal symptoms from age of onset for the first diagnosable mood episode.

A baseline *composite clinical presentation variable* was created by calculating dummy codes for manic symptom severity, C-GAS scores, and prodrome duration. Dummy codes were assigned after calculating baseline distribution sample quartiles. For example, a code of '0' was recorded for C-GAS scores in the lowest quartile; a code of '1' was recorded for C-GAS scores in the second quartile; a code of '2' was recorded for C-GAS scores in the third quartile; and a code of '3' was recorded for C-GAS scores in the fourth quartile. Therefore, the dummy-coded C-GAS ranged from 0–3. Dummy coding for prodrome duration and manic symptom severity was done similarly. Finally, a composite score for clinical presentation was calculated by summing the three dummy coded variables. Thus, clinical presentation composite scores could range from 0–9, with higher numbers indicating greater impairment.

Family environment

The Coddington Life Events Scale for Children (LES) (31) was administered at baseline to document stressful life events in the family prior to study entry.

The Expressed Emotion Adjective Checklist (EEAC) (32) was administered to assess baseline parent-child dyadic interactions. The lowest (i.e., worst) score was used if both caregivers completed this measure.

A *composite family environment variable* was created by calculating dummy codes for the LES and EEAC in a similar manner to the clinical presentation dummy codes. The family environment composite score had a possible range of 0–6, with higher numbers indicating a more problematic family environment.

Family history variables

The Ohio State Adaptation of the Family History–Research Diagnostic Criteria (Fristad MA, unpublished document, The Ohio State University, 1986) was used to collect baseline information concerning family history of symptoms (given a score of 1) and diagnoses (given a score of 2) of 13 major psychiatric disorders in the probands' first and second-degree relatives. Adaptations from the original Family History–Research Diagnostic Criteria (FH-RDC) (33) were inclusion of eating disorder and anxiety disorder criteria using the same format as the original instrument. From this, four summary variables were created for each child: (i) *Parental bipolar disorder scale*: (biological mother's bipolar score + biological father's bipolar score)/number of biological parents with FH-RDC information. This score was missing for two participants from adoptive families with no known birth parent mental health history. (ii) *Second degree relatives' bipolar disorder scale*: $2 \times$ [(number of maternal and paternal second degree relatives with diagnosis of bipolar

disorder) + (number of maternal and paternal second degree relatives with symptoms of bipolar disorder)]/number of second degree relatives with FH-RDC information. This score was missing for three participants who had an unknown extended family mental health history. (iii) *Loaded family history of major affective disorder scale*: (sum of mother's and father's score on bipolar disorder, depression, and schizoaffective disorder) + $2 \times$ [(sum of number of maternal and paternal second degree relatives with diagnosis of bipolar disorder, depression, and schizoaffective disorder) + (sum of number of maternal and paternal second degree relatives with symptoms of bipolar disorder, depression, and schizoaffective disorder)]/(number of parents with FH-RDC information + number of second degree relatives with FH-RDC information). The information on family history of major affective disorder in parents and second degree relatives was missing for two participants whose parental information was missing.

Severity of parental mood symptoms was measured using the Hamilton Rating Scale for Depression (HAM-D) (35) and the MRS. Both were administered at baseline to assess current severity of mood symptoms in one or both parents. If both parents reported symptoms, the highest reported level on each instrument was used.

Composite family history variable—A composite family history variable was created in a comparable manner to the two previous composite variables by calculating dummy codes for FH-RDC, HAM-D, and MRS. The family history composite score could range from 0–9, with higher numbers indicating more familial loading.

Statistical analyses

For Hypothesis 1, a one-way ANOVA with diagnostic group (DSD+TMS, DSD, and BPSD) as the independent variable and C-GAS score as the dependent variable was used to compare C-GAS scores among the three groups. As the three diagnostic groups marginally differed on age and IQ, an additional analysis was conducted including these two variables as covariates. Tukey's post-hoc analysis was conducted to complete pairwise comparisons (DSD+TMS versus DSD; DSD+TMS versus BPSD; DSD versus BPSD). For Hypotheses 2 and 3, Fisher's Exact Tests (FET) were used to compare the proportion of conversion rates for each group. For Hypothesis 4, a two-sample *t*-test was conducted to assess whether the mean level of impairment in clinical presentation, family environment, or family history at Time 1 (as measured by the composite variables) differed between the two groups. For secondary hypotheses, a two-sample *t*-test was conducted to assess whether the average of the composite variables' components differed between the two groups. As these were exploratory hypotheses, corrections were not made for multiple comparisons. Hypotheses 2, 3, and 4 compared only DSD and DSD+TMS. As these two groups did not differ on age [$t(31) = -0.92$, $p = 0.36$] and IQ [$t(31) = 0.52$, $p = 0.60$], no further analyses were conducted by controlling these covariates.

Hypotheses 2, 3, and 4 were also run using ITT analyses. Effect sizes (Cohen's *d*, Cramer's *V*, and partial eta squared) were calculated for all hypotheses. Power analyses using Dean and Voss' methodology (36) were calculated to determine the sample sizes needed to test Hypotheses 1 and 4 in future studies.

Results

Frequency of conversion

Overall, 39.4% of the sample converted to a BPSD by 18-month follow-up. Twelve children converted from DSD+TMS to BPSD over the 18-month follow-up (five converted by Time 2, five more by Time 3, and two more by Time 4). Three children converted to BP-I, five to

BP-II, three to BP-NOS, and one to substance-induced mood disorder with manic features. One child converted from DSD to BPSD over the 18-month follow-up; this child converted to BP-NOS by Time 3. Frequency of manic symptoms endorsed with a score of ≥ 2 on the MRS was tabulated to contrast baseline profiles of children with DSD+TMS with their profiles at time of conversion (see Table 3). Average endorsement for the 11 MRS items increased from 30–47% from baseline to time of conversion.

C-GAS comparison

A one-way ANOVA revealed that the three diagnostic groups (DSD+TMS, DSD, and BPSD) did not differ significantly on Time 1, C-GAS scores [$F(2,162) = 1.33$, $p = 0.27$]; however, mean C-GAS scores were in the anticipated direction (DSD+TMS: mean $\pm$ SD = 44.8 ± 7.1 ; DSD: mean $\pm$ SD = 46.5 ± 7.0 ; BPSD: mean $\pm$ SD = 43.1 ± 8.8). The observed power of this test was 30%. A total of 55 participants per group would be needed to test this hypothesis, assuming power of 0.8 and alpha level of 0.05. As differences in age and IQ between the three diagnostic groups at baseline approached significance, analyses were rerun using age and IQ as covariates; C-GAS scores still did not differ significantly between the groups when making these adjustments [$F(4,159) = 0.45$, $p = 0.64$].

Conversion rates among groups

DSD+TMS children converted to BPSD by Time 4 at a higher rate than children with DSD (see Table 4, $FET = 8.50$, $p = 0.01$). The strength of association between conversion rates and diagnosis status of the group was medium (Cramer's $V = 0.55$). Results were similar for the ITT analysis (see Table 4, $FET = 20.36$, $p = 0.000$).

Impact of treatment on conversion rates

The WLC group converted to BPSD at Time 3 at a four-fold higher rate than the IMM group (see Table 5, $FET = 6.61$, $p = 0.03$). The strength of association between conversion rates and treatment condition was medium (Cramer's $V = 0.50$). Results trended toward significance for the ITT analysis (see Table 5, $FET = 5.44$, $p = 0.07$).

Risk factors for conversion

Clinical presentation, family environment, and family history were all more problematic in the converted group compared to the non-converted group, but these differences were not statistically significant [see Table 6: $t(23) = 1.35$, $p = 0.19$; $t(22) = 0.42$, $p = 0.67$; $t(21) = 1.01$, $p = 0.32$, respectively]. However, power was quite low for these analyses, given the small sizes of the subsamples (clinical presentation, power 30%; family environment, power 7%; family history, power 16%). A total of 55 participants per group would be needed to test this hypothesis, assuming power of 0.8 and alpha level of 0.05. Results were similar for ITT analyses [clinical presentation: $t(35) = -0.94$, $p = 0.35$; family environment: $t(31) = -0.53$, $p = 0.60$; family history: $t(32) = -0.53$, $p = 0.38$].

Secondary analyses

Only one of ten components of the three composite variables differed significantly between converters and non-converters. Baseline C-GAS scores indicated more impairment in the converted group than the non-converted group [$t(23) = -2.84$, $p = 0.009$] (see Table 6). However, eight of ten comparisons were in the predicted direction.

Due to small sample sizes, a nonparametric procedure, the Mann-Whitney U test was conducted to determine whether the converted group and the non-converted group were from different sample distributions. Again, a significant difference was noted in the sample distributions for C-GAS scores ($U = 34.5$, $p = 0.02$).

Post-hoc analyses

Several additional clinical features were examined in relation to conversion. First, the potential relationship between age, time of conversion, and type of BPSD was examined. Younger (i.e., 8–10) versus older (i.e., 11–12) children were equally likely to convert by 6, 12, or 18 months and type of diagnosis at time of conversion (i.e., BP-I, BP-II, BP-NOS) did not differ based on age.

Second, the potential impact of medication on conversion was explored. Detailed medication histories were available for participants at baseline and 12 months. Use of antidepressants, stimulants, anti-obsessionals, mood stabilizers, antipsychotics, beta-blockers, benzodiazepines, atomoxetine and herbal remedies was examined. No pattern was detected between usage of any of these medications at baseline or 12 months and conversion status.

Discussion

Conversion to BPSD in this sample of depressed children was 39.4%, consistent with previously reported rates. Those with DSD+TMS were at particular risk, with a 48% conversion rate over an 18-month follow-up period. Children with DSD converted at a 12.5% rate. These relatively high conversion rates over a brief time interval highlight the importance of teaching parents how to monitor for the emergence of prodromal manic symptoms in children diagnosed with depression, as well as careful monitoring by the clinicians treating these children. Of note, irritability and disruptive, aggressive behavior were prominent prodromal manic symptoms in the children who ultimately converted. Those symptoms, which are not unique to BPSD, actually declined somewhat in frequency once the child met diagnostic criteria for a BPSD, while endorsements for other more ‘classic’ manic symptoms (e.g., elevated mood, decreased need for sleep) increased.

Contrary to our hypothesis, participation in MF-PEP was associated with a four-fold reduction in risk for conversion. This suggests that psychoeducational interventions may be protective. These findings are speculative and clearly require replication, but potential mechanisms of action might include improvement in functioning due to families becoming better consumers of mental health care, decreased stress via provision of social support, or improved functioning via the skills development promoted in MF-PEP.

Overall clinical presentation, family environment, and family history at baseline did not differ significantly between those children who did convert to BPSD over 18-months and those who did not. However, C-GAS scores (one component of overall clinical presentation) did differ significantly between the two groups. It is important to keep in mind this was an exploratory study, sample sizes for subgroup comparisons were quite small, reducing power to adequately test hypotheses, and corrections for multiple comparisons were not made. Examination of these factors in prospective, large-scale studies [such as the Bipolar Offspring Study (BIOS), COBY, and Longitudinal Assessment of Manic Symptoms LAMS]] of children at high risk for developing BPSD is needed to clarify what role, if any, they may play in the onset of diagnosis.

Limitations and directions for future research

There were several limitations in the present study. Most importantly, DSD+TMS and DSD sample sizes were small at baseline ($n = 37$ and 13 , respectively) and even smaller at follow-up ($n = 25$ and 8 , respectively). As the DSD+TMS group was further divided into converted and non-converted subsamples ($n = 12$ and 13 , respectively), power to test hypotheses was minimal. Second, the restricted racial demographics of the present study (i.e., predominantly white) limits the generalizability of these findings to other populations. Third, as these were exploratory hypotheses, corrections were not made for multiple comparisons. Fourth, 18-

months is a relatively brief period in which children might convert. Future studies should examine risk factors associated with conversion over a longer follow-up period.

Despite these clear limitations, this study provides evidence that depressed children do convert to BPSD at a notable rate, and that TMS are a risk factor for conversion. An additional intriguing finding, which clearly warrants additional investigation, is the suggestion that psychoeducational psychotherapy may be protective for depressed children in staving off potential conversion to BPSD. Future research should assess the influence of pharmacotherapy and psychoeducational psychotherapy on transient manic symptoms and subsequent conversion to BPSD.

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Figure 1.

Participant status over 18-month follow-up. DSD = depressive spectrum disorder; TMS = transient manic symptoms; BPSD = bipolar spectrum disorder. **Hypothesis 1:** DSD+TMS (n = 37), DSD (n = 13), BPSD (n = 115). **Hypothesis 2:** DSD+TMS (n = 25), DSD (n = 8). **Hypothesis 3:** DSD+TMS [(n = 27): immediate treatment group = 12 and one-year wait-list control group = 15]. **Hypothesis 4:** converted (n = 12) and non-converted (n = 13). Intent-to-treat analysis: 12 *Time 4* dropouts from DSD+TMS group and 5 *Time 4* dropouts from DSD group had their last observation carried forward to impute *Time 4* missing data (DSD +TMS group = 12 converters and 25 non-converters; DSD group = 1 converter and 12 non-converters).

Table 1

Diagnostic criteria for transient manic symptoms (TMS)

Diagnostic criteria	
<ul style="list-style-type: none">Any one or more of the following symptoms:<ul style="list-style-type: none">– elated mood, grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increase in goal directed activity, excessive involvement in pleasurable activities with high potential for painful consequencesThese mood symptoms can be differentiated from attention-deficit hyperactivity disorder symptoms with reasonable certaintyThere are 1–3 manic-like episodes of moderate to severe intensity lasting four or more hours <u>or</u> there have been ≥ 2 brief episodes of two to four hours in durationEvidence of functional impairmentDoes not meet criteria for bipolar I or II disorder, bipolar disorder-not otherwise specified, or cyclothymia	

Table 2

Baseline characteristics of participants with depressive spectrum disorder (DSD) + transient manic symptoms (TMS), DSD, and bipolar spectrum disorder (BPSD)

Baseline characteristics	DSD+TMS (n = 37)	DSD (n = 13)	BPSD (n = 115)	p-value
Male gender, n (%)	28 (76)	10 (77)	83 (72)	0.88
Age, years, mean (SD)	10.1 (1.3)	10.4 (1.4)	9.7 (1.3)	0.08
Parent's age, years, mean (SD)	40.9 (9.6)	37.8 (8.2)	39.8 (6.3)	0.79
Race, n (%)				0.73
White	33 (89)	12 (92)	105 (91)	
Non-white	4 (11)	1 (8)	10 (9)	
Family structure, n (%)				0.77
Married biological parents	14 (38)	4 (31)	53 (46)	
Step-family	6 (16)	2 (15)	25 (22)	
Single parent	8 (22)	4 (31)	19 (16)	
Adoptive parents	3 (8)	1 (8)	8 (7)	
Foster family and other	6 (16)	2 (15)	10 (9)	
Family income, n (%)				0.91
Less than \$40,000	14 (38)	6 (46)	34 (30)	
\$40,000–80,000	15 (40)	3 (23)	41 (36)	
Greater than \$80,000	8 (22)	4 (31)	40 (34)	
Comorbid disorders, n (%)				
Behavior disorders	36 (97)	12 (92)	112 (97)	0.40
Anxiety disorders	26 (70)	9 (69)	78 (68)	0.96
Intelligence quotient, mean (SD)	112.2 (17.1)	109.3 (9.2)	106.0 (15.1)	0.10

Align values by left parenthesis.

Table 3

Frequency (percent) of manic symptoms at Time 1 and Time of conversion for the converted group

Manic symptoms	Time 1	Converted Time-point ^a	Change Direction ^b
Elevated mood	8	58	↑
Irritability	83	75	↓
Content	25	42	↑
Sleep	8	25	↑
Language-thought disorder	33	25	↓
Speech (rate and amount)	50	75	↑
Increased motor activity/energy	0	67	↑
Sexual interest	8	25	↑
Disruptive-aggressive behavior	75	58	↓
Appearance	17	33	↑
Insight	25	33	↑
Average item endorsement	30	47	↑

Converted group = depressive spectrum disorder (DSD) + transient manic symptoms (TMS) who converted to bipolar spectrum disorder (BPSD).

^a Five subjects converted at Time 2, five at Time 3, and two at Time 4.

^b From Time 1 to converted time-point.

Table 4

Conversion rates to bipolar spectrum disorder (BPSD) at 18-month follow-up of participants diagnosed at baseline with depressive spectrum disorder (DSD) + transient manic symptoms (TMS), and DSD

Baseline diagnostic group	18-month diagnosis		
	DSD+TMS n (%)	DSD n (%)	BPSD n (%)
Study completers ^a			
DSD+TMS (n = 25)	9 (36.0)	4 (16)	12 (48.0)
DSD (n = 8)	1 (12.5)	6 (75)	1 (12.5)
Intent-to-treat analysis ^b			
DSD+TMS (n = 37)	20 (54)	5 (14)	12 (32)
DSD (n = 13)	1 (8)	11 (84)	1 (8)

^a p = 0.01, Fisher's Exact Test;

^b p = 0.000, Fisher's Exact Test.

Table 5

Conversion rates to bipolar spectrum disorder (BPSD) at 12-month follow-up for the immediate treatment condition (IMM) and one-year wait-list control (WLC) condition groups diagnosed with depressive spectrum disorder (DSD) + transient manic symptoms (TMS) at baseline

12-month diagnosis			
DSD+TMS (baseline)	DSD+TMS n (%)	DSD n (%)	BPSD n (%)
Study completers ^a			
IMM (n = 12)	5 (42)	5 (42)	2 (16)
WLC (n = 15)	5 (33)	1 (7)	9 (60)
Intent-to-treat analysis ^b			
IMM (n = 17)	10 (59)	5 (29)	2 (12)
WLC (n = 20)	9 (45)	2 (10)	9 (45)

^a p = 0.03, Fisher's Exact Test;

^b p = 0.07, Fisher's Exact Test.

Table 6

Baseline differences on clinical presentation, family environment, family history, and their components between the converted and non-converted groups

Variables (components)	Converted (n = 12)		Non-converted (n = 13)		p-value	Power ^d	d ^b	Effect size ^c
	Mean	(SD)	Mean	(SD)				
Clinical presentation								
MRS score	3.9 (1.6)		3.1 (1.5)		0.19	30%	0.54	M
Prodrome duration	15.5 (6.9)		12.2 (7.8)		0.28	19%	0.44	M
C-GAS score	38.0 (29.7)		42.4 (25.7)		0.70	7%	-0.16	S
	43.8 (5.8)		49.5 (4.1)		0.009	80%	-1.14	L
Family environment								
Life events	3.0 (1.7)		2.7 (1.8)		0.67	7%	0.17	S
Parent-child dyadic interactions	172.7 (160.0)		174.0 (121.3)		0.98	5%	-0.009	>S
	18.3 (25.3)		28.7 (26.6)		0.32	12%	0.40	M
Family history								
Parental bipolar disorder	3.7 (1.7)		2.9 (2.1)		0.32	16%	0.05	S
2 nd degree bipolar disorder	0.4 (0.7)		0.2 (0.4)		0.49	10%	0.29	M
Loaded history ^d	0.9 (1.7)		0.8 (1.4)		0.80	6%	0.11	S
	6.4 (3.5)		5.0 (2.7)		0.29	5%	0.45	M
MRS score (parent)	2.1 (2.6)		1.5 (2.1)		0.52	9%	0.02	S
HAM-D score (parent)	8.7 (10.2)		5.5 (6.5)		0.34	15%	0.04	S

Higher scores indicate greater impairment except for Children's Global Assessment Scale (C-GAS) scores and parent-child dyadic interactions for which lower scores indicate greater impairment. MRS = Mania Rating Scale; HAM-D = Hamilton Rating Scale for Depression.

^aObserved power calculated using an alpha of 0.05.

^bCohen's effect size.

^cS = small $d \leq 0.20$, M = medium $d = > 0.20 < 0.80$, L = large $d \geq 0.80$.

^dLoaded family history major affective disorder scale.