Clinical Course of Children with a Depressive Spectrum Disorder and Transient Manic Symptoms

Dissertation

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Abstract

The present study (Multi-family Psychoeducation Group) provides 18-month longitudinal follow-up of children diagnosed with depressive spectrum disorder (DSD; major depressive disorder and/or dysthymic disorder) who present with clearly demarcated transient manic symptoms (TMS) of insufficient number or duration to be diagnosed with a bipolar spectrum disorder (BPSD; Bipolar-I, Bipolar-II, Cyclothymia, Bipolar-Not Otherwise Specified). Assessments were conducted at four time points, baseline (Time 1), 6 months (Time 2), 12 months (Time 3) and 18 months (Time 4). At Time 1 there were 115 participants in the BPSD group, 37 in the DSD + TMS group, and 13 in the DSD group. Due to sample attrition in the DSD + TMS and DSD groups, at Time 2 these two groups had 38 participants, at Time 3, 35 participants, and at Time 4, 33 participants. Measures that assessed socio-demographic variables, IQ (Kaufman Brief Intelligence Test), mood and co-morbid diagnoses (Children’s Interview for Psychiatric Syndromes – Child and Parent form [ChIPS/P-ChIPS]), clinical presentation (Mania Rating Scale, Children’s Depression Rating Scale – Revised, Children’s Global Assessment Scale, duration of prodromes), family environment (Coddington’s Life Events Scale, Expressed Emotion Adjective Checklist) and family history (Family History Research Diagnostic Criteria, Parental Mood Severity Index [calculated using Hamilton Rating Scale for Depression and Mania Rating Scale]) were collected at Time
1. I hypothesized that: 1) at Time 1, children with DSD + TMS will have lower C-GAS scores than children with DSD but higher scores than children with BPSD; 2) children with DSD + TMS at Time 1 will convert to BPSD at follow-up at a higher rate than children with DSD at Time 1; 3) conversion rates differed will not differ for DSD + TMS participants regardless of treatment status; 4) children with DSD + TMS at Time 1 who convert to BPSD at follow-up (converted group) will have greater impairment in clinical presentation, family environment and/or family history compared to children with DSD + TMS at Time 1 who do not convert (non-converted group). A secondary hypothesis was: the converted group will be more impaired on components of clinical presentation, family environment and/or family history than the non-converted group. Hypothesis 1, 3 and 4 were not supported. Hypothesis 2 was supported. The conversion rate from DSD + TMS to BPSD was 48% whereas the conversion rate from DSD to BPSD was 12.5% suggesting that TMS in a DSD population is a risk factor for conversion. This is particularly important, as pharmacologic treatments for children with depression and/or ADHD can destabilize children with bipolar disorder (Geller et al., 1992; Reichart & Nolen, 2004). Contrary to the hypothesis, for DSD + TMS participants, the one year wait-list control group (WLC) conversion rate was 60% whereas the immediate treatment group (IMM) conversion rate was 16% suggesting that psychosocial treatment may be beneficial. The secondary hypothesis was supported only for C-GAS scores. The converted group had lower C-GAS scores at Time 1 than the non-converted group. Clinical descriptions of converters and non-converters, limitations, clinical implication and future research ideas are discussed.
Dedication

Dedicated to my loving aai and baba,

Aruna and Bhaskar Nadkarni
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Chapter 1: Introduction

Bipolar disorder (BPD) is a controversial diagnosis in children, and relatively little is known about its longitudinal course, particularly whether childhood manifestations are comparable to the adult form of the disorder (American Academy of Child and Adolescent Psychiatry, 2007). Some adult mood researchers (e.g., Akiskal & Benazzi, 2006; Benazzi, 2007) hypothesize that unipolar and BPD (mainly Bipolar II [BP-II]) lie on a dimensional continuum as they share several common features (age at onset, atypical depressive features, depressive mixed state, and number of recurrences) and their research has begun to focus on a wide array of bipolar spectrum disorders (BPSD; Bipolar I [BP-I], BP-II, Cyclothymia, Bipolar-Not Otherwise Specified [BP-NOS]).

Even less is known about the full spectrum of BPD in children. Only one longitudinal study has examined manic symptoms in children diagnosed with BPSD (Axelson, Birmaher, Strober, Gill, Sylvia et al. 2006). No studies to date have assessed longitudinally the clinical importance of transient manic symptoms (TMS) in children with depressive spectrum disorder (DSD; Major Depressive Disorder [MDD] and/or Dysthymic Disorder [DD]) to determine whether transient subthreshold manifestations later progress to a recognized BPSD. Retrospective studies in adult populations indicate that 50% to 60% of adults with BPD report their initial onset of mania or depression
occurred prior to 19 years of age (Hirschfeld, Lewis & Vornik, 2003; Chengappa, Kupfer, Frank, Houck, Grochocinski, Cluss, & Stapf, 2003). Moreover, adults with childhood-onset BPD are ill 16 years, on average, before getting treatment (Leverich et al., 2007). Delays in the diagnosis and proper treatment of BPD may result in poor prognosis for childhood-onset BPD (Leverich et al., 2007). Early detection of BPD can shorten the time to initiate treatment and minimize the detrimental course of this illness (Leverich et al., 2007).

In this dissertation, I review: 1) prevalence rates of BPD; 2) retrospective studies of adults with BPD; 3) literature on the rate of conversion to bipolarity in adults with unipolar disorder; 4) existing studies that assess the rate and predictors of bipolarity in children and adolescents diagnosed with MDD; 5) studies that assess differing features between unipolar and bipolar mood disorders; 6) literature assessing prodromal symptoms of BPD; 7) genetic studies on unipolar and BPD; and 8) precipitants that may influence the onset of mania. After summarizing the extant literature, I describe the current study’s method and hypotheses.

My dissertation examined 18-month longitudinal follow-up data of children diagnosed with DSD who present with transient manic symptoms (TMS). TMS are defined as manic-like symptoms of insufficient duration or number to warrant a diagnosis of BPSD. Hypotheses in this study examined: 1) the level of global impairment for children with BPSD, DSD, and DSD + TMS; 2) the rate of conversion from DSD + TMS to BPSD; 3) risk factors [prodromal manic symptoms, prodromal duration, the level of global impairment, life events, a critical and hostile family environment, family history (biological parents and second degree relatives) of major affective disorder (BPD,
depression, schizoaffective disorder), current levels of parental depression and mania] associated with the rate of conversion in DSD + TMS population. Finally, I interpret and discuss my results, provide clinical descriptions of converters and non-converters, clinical implications, limitations, and goals for future research.

Prevalence Rates of Bipolar Disorder

Lifetime prevalence estimates for BPD in the adult population are 6.4% (0.8% for manic episode, 0.5% for hypomanic episode, and 5.1% for subthreshold) (Judd & Akiskal, 2003). No data are provided for cyclothymia. Adolescent data are similar. Rates for both BP-I and BP-II are 1%; an additional 5.7% experience core manic symptoms that do not meet diagnostic criteria for a manic episode (Lewinsohn, Klein & Seeley, 1995). One longitudinal epidemiological study (The Great Smoky Mountain study) suggests a lifetime prevalence rate of 3.3% for severe mood dysregulation (Brotman, Schmajuk, Rich, Dickstein, Guyer, Costello, Egger, Angold, Pine & Leibenluft, 2006), defined “extreme, impairing, and chronic irritability, accompanied by hyperarousal symptoms” (pg. 991). Severe mood dysregulation may be seen as a subtype of the broad phenotype of pediatric BPD (Brotman et al., 2006). Despite limited research on the prevalence rates of BPD in children, studies indicate this condition exists (Youngstrom, Findling, Youngstrom & Calbrese, 2005). Next I discuss retrospective studies of adults that confirm the onset of BPD in childhood and adolescence.

Retrospective Studies of Adults with Bipolar Disorder

Retrospective studies indicate that 50% to 60% of adults with BPD report an onset of mania or depression prior to 19 years of age (Chengappa, Kupfer, Frank, Houck, Grochocinski, Cluss, & Stapf, 2003; Hirschfeld, Lewis and Vornik, 2003; Leverich, et
Chengappa and colleagues (2003) analyzed data from self-identified subjects with BPD \( N = 1,218 \) from the Stanly Center Bipolar registry in two birth cohorts (1900 through 1939 and 1940 through 1959). Their findings indicated: (1) adolescent onset was common, 75% of the sample had their first episode by age 29, with a peak (approximately 23%) between 15 and 19 years; (2) a birth cohort effect was evident. While 37% of the 1900-1939 birth cohort had their first episode before age 19, 53% of those subjects from the 1940-1959 birth cohort had their first episode before age 19. Similarly, 15.6% of subjects born between 1900 through 1939 had a very young age of onset (age 14 or younger). This rate nearly doubled to 28.9% for those born in 1940-1959. Subjects born between 1940 and 1959 reported a median age of onset of first episode almost five years earlier than subjects born between 1900 and 1939 \( (median \pm SD = 19.0 \pm 9.9 \text{ versus } 23.5 \pm 10.4) \). Several reasons may explain an earlier age of onset in the later birth cohort (Goodwin & Jamison, 2007, p. 121 & 699; Chengappa et al., 1993). Fifty years ago, some patients with early-onset may have been diagnosed with schizophrenia instead of BPD, as the criteria for the diagnosis of BPD may have been less broad (Goodwin & Jamison, 2007, p. 121; Chengappa et al., 1993). The pharmacological revolution associated with lithium led to the development of current diagnostic systems, Diagnostic Statistical Manual (DSM)–IV and the International Classification of Diseases (ICD)-10 (Goodwin & Jamison, 2007, p. 699), which may explain earlier detection of BPD. Increased use of antidepressants and stimulants may provoke earlier onset in children and adolescents susceptible to BPD (Goodwin & Jamison, 2007, p. 121). This is consistent with evidence suggesting antidepressant medications may cause cycle acceleration and/or induce manic symptoms (Goodwin &
 Increased use of recreational drugs and alcohol may lead to earlier onset of symptoms in youth; studies are needed to test this hypothesis (Goodwin & Jamison, 2007, p. 121); (3) Subjects whose parents had major depressive disorder, BPD or schizophrenia had a first episode an average of four to five years earlier than subjects without parental history of these disorders. Finally, the registry study confirmed that BPD is equally likely to present initially with depression. Fifty percent of all participants had a first episode of depression, later followed by a manic episode.

Similar findings were reported by Hirschfeld and colleagues (2003), who conducted a retrospective survey of 600 members of the National Depressive and Manic-Depressive Association who self-identified as having BPD. Their results indicated: (1) age of onset typically occurred prior to adulthood; 60% of respondents had their onset prior to age 19. One-third reported age of onset at 15 years or younger. Another quarter of the sample (27%) reported an age of onset between ages 15 and 19. A minority (39%) reported an age of onset at 20 years or later; (2) a known family history of BPD was common, 45% of all respondents indicated a family history of BPD. Respondents had, on average, 2.1 family members diagnosed with BPD. Most (82%) of these relatives had been treated for BPD; (3) a majority of respondents (70%) had experienced at least one impairing manic symptom for some time prior to their diagnosis. These included erratic sleeping, elevated mood, racing thoughts, increased speech, impulsiveness, increased physical and/or mental activity, and poor judgment. Of note, two-thirds (67%) of respondents experienced excessive irritability and aggressive behavior, while 57% experienced reckless behavior; (4) misdiagnosis was common. When respondents were asked if they had been misdiagnosed, over two-thirds (69%) of
the sample reported having been misdiagnosed, most frequently with unipolar depression. Further, those who were misdiagnosed reported consulting an average of four physicians before getting the correct diagnosis. Over one-third who had been misdiagnosed did not receive a correct diagnosis for 10 or more years after seeking treatment. This can be a problem, as treatment with an inappropriate medication (e.g., stimulants or SSRIs) can result in a poor prognosis in adults with childhood-onset BPD; (5) the illness caused hardship on the individual, his or her family and career. Relationship problems (80%), financial difficulties (55%), physical health problems (46%), substance abuse (37%), and job and school related problems (73%) were noted.

Both of these studies have limitations. First, they used self-identified patients with BPD. Second, their retrospective design is susceptible to faulty recall. Therefore, findings need to be interpreted with caution. However, a third study (Leverich et al., 2007) that utilized patients diagnosed using the SCID (Structured Clinical Interview for DSM-IV Axis I disorders; Spitzer, Williams, Gibbon, & First., 1996) had similar findings. Leverich and colleagues (2007) retrospectively examined 480 adult patients ($M \pm SD$ age = 42.5 ± 11.6) diagnosed with BP-I and BP-II to carefully document their age of onset. They then assessed various outcomes in relation to age of onset. After study admission, a full year of prospective daily clinician ratings were collected. They found that: (1) half the sample experienced onset in childhood or adolescence, 36% had an adolescent onset and 14%, a prepubertal onset; (2) childhood-onset was associated with the longest delays in receiving treatment compared with adolescent-onset ($M \pm SD$ years = 16.8 ± 10 versus 11.5 ± 10); (3) childhood-onset was associated with the highest incidence of parental history of BPD (47%) and of unipolar depression (52%). As age of
onset increased, these percentages declined; (4) environmental adversity (physical and sexual abuse) was higher in childhood and adolescent onset of BPD; (5) childhood-onset was associated with a more pernicious course compared to adult-onset in terms of severity of depression, severity of mania, and number of episodes. Retrospectively, these patients reported more episodes, more comorbidity and more rapid cycling. Prospectively, they endorsed more severe mania, more depression, and fewer days not in episode.

In conclusion, these studies indicate that half or more of adults with BPD reported their age of onset prior to 19 years. A sizable minority (14-33%) reported their age of onset prior to 14 to 15 years. Thus, prepubertal and adolescent onset of BPD is not rare. Prepubertal onset was associated with a significant delay in receiving treatment ($M = 16$ years). Thus, early-onset is often accompanied by many years of significant impairment to the individual, his or her family life and career (Hirschfeld, Lewis & Vornik, 2003).

Half experienced a depressive episode first, highlighting the importance of tracking manic symptoms in individuals with depression. Early age of onset was associated with a more pernicious course. Family history of mood disorders was common. A majority of respondents experienced impairing symptoms prior to diagnosis. Misdiagnosis of unipolar depression was common. Next, I review the literature on rates of conversion to BPD in adults diagnosed with unipolar depression.

Rate of Conversion to Bipolarity in Adults with Unipolar Disorder

Several researchers have assessed the risk of converting to BPD in adult patients diagnosed with unipolar depression (Akiskal et al., 1995; Angst, Sellaro, Stassen & Gamma, 2005; Goldberg, Harrow & Whiteside, 2001). Akiskal and colleagues (1995)
prospectively assessed 559 outpatients. Over the course of 11 years, 12.5% of the subjects developed BPD, 3.9% converted to BP-I and 8.6% converted to BP-II. Goldberg and colleagues (2001) prospectively assessed 74 adult inpatients ($M \pm SD$ age $= 23.0 \pm 3.8$) diagnosed with major depression after their discharge. Nearly half (45%) experienced either a manic (19%) or hypomanic (27%) episode during the 15-year study period. Patients who had psychotic features at the index episode were more likely to experience mania or hypomania at follow-up compared to patients with depression without psychotic features.

Angst and colleagues (2005) prospectively assessed 406 inpatients with major depression. Over an average of 23.4 years, one-half converted to either BP-I (32.1%) or BP-II (17.9%). Patients with more than six depressive episodes converted to BPD at 3.6 times the rate of those with fewer episodes. Conversion to BPD was three times higher for those with a positive family history of mania.

Rates of conversion from unipolar disorder to subsequent BPD in these studies ranged from 12.5% in an outpatient sample followed for 11 years to 45-50% for an inpatient sample followed for 15 to 23 years. Clinical features associated with conversion include: depression with psychotic features, more than six depressive episodes and a positive history of mania. Next, I review the conversion rate and predictors of bipolarity in youth with MDD.

*Rate and Predictors of Bipolarity in Youth with MDD*

Several prospective studies have assessed the rate and predictors of bipolarity in children and adolescents diagnosed with MDD (Strober & Carlson, 1982; Geller, Fox &
Clark, 1994). Others have prospectively assessed adults with BPD who had prepubertal MDD (Geller, Zimerman, Williams, Bolhofner and Craney, 2001).

Strober and Carlson (1982) prospectively studied 60 adolescents (ages 13 to 16 years) who were hospitalized for major depression and had no preexisting symptoms of mania at the time of admission. Over three to four years, 20% developed BP-I. Predictors of switching to BPD were: (1) rapid symptom onset; (2) psychomotor retardation; (3) mood-congruent psychotic features; (4) a family history of BPD, in particular, a three-generation history of psychiatric illness; and (5) pharmacologically induced mania.

Geller and colleagues (1994) assessed predictors of BP-I and BP-II in a sample of 79 subjects aged 6 to 12 years with non-delusional DSM-III diagnoses of MDD. These subjects were compared over 2 to 5 years to 31 community control children matched for age, socioeconomic status and gender. In a two–to-five year follow-up, nearly one-third of the sample developed BP-I ($n = 10$) or BP-II ($n = 15$). Their average age at conversion was 11.2 years; the majority (80%) was prepubertal. No control participant developed BPD. A loaded family history of major affective disorder (three or more first-or second-degree relatives with mania, BP-I, major depression, schizoaffective disorder) resulted in a six-fold increase in the risk of developing BP-I. Loaded family history was not associated with BP-II outcome. Prior or current use of tricyclic antidepressants and atypical depressive features (hypersomnia, hyperphagia, psychomotor retardation and mood reactivity – alone or in combination) did not predict which children switched to BPD. Finally, atypical depressive features (singly or in combination) were not predictive of bipolar outcome.
Geller and colleagues (2001) conducted a second follow-up study assessing 72 subjects with prepubertal MDD and 28 normal comparison controls when their sample became adults ($M \pm SD$ age = 20.7 ± 2.0) (Geller, Zimerman, Williams, Bolhofner and Craney, 2001). At this follow-up, which averaged nearly ten years after initial enrollment (9.9 years), nearly half their sample (48.6%) converted to a bipolar diagnosis (BP-I, BP-II, or hypomania) compared to the 7.1% of the controls. Finally, a family history of mania in parents and/or grandparents predicted a BP-I outcome.

These three studies indicate conversion from MDD to BP-I and BP-II in prepubertal children and adolescents is relatively common, ranging from 20% to 49%, depending on the length of follow-up. Thus, diagnostic stability is low for childhood-onset MDD (Benazzi, 2007). These rates likely underestimate rates of conversion to BPSD. Results were similar despite differences in sample characteristics that included an inpatient population and outpatients without psychotic features. Different predictors (a family history of BPD, rapid symptom onset, psychomotor retardation, mood congruent psychosis, pharmacologically induced mania) were identified by different researchers as predictors of bipolar onset in children and adolescents diagnosed with MDD.

These studies have important clinical implications. First, children with MDD and their families should be alerted to the possibility of developing BPD and taught to recognize early symptoms associated with mania (Geller, Tillman, James & Bolhofner, 2004). Second, clinicians should be aware that children with MDD are at high risk for converting to BPD and should monitor for emergent prodromal symptoms. Third, due to high rates of conversion, significant caution should be taken when prescribe
antidepressants to children with MDD, as antidepressants may worsen childhood mania (Geller, Cooper, Graham, Fetner, Marsteller & Wells, 1992). Finally, predicting which children will convert to BPD after their index MDD episode is of vital importance to clinicians and physicians (Akiskal et al., 1995). Next, I review differing aspects between depression and BPD. Some of these aspects can be used to identify patients who are likely to subsequently develop BPD.

**Distinguishing Features between Depression and BPD**

“False unipolar” patients are patients initially classified as unipolar but who subsequently experience a manic or hypomanic episode (Goodwin & Jamison, 2007, p. 14). False unipolar patients are not patients misdiagnosed with unipolar disorder rather they are patients who subsequently develop BPD. These patients are more similar to patients with BPD than patients with ‘pure’ unipolar depression (patients with ‘pure’ unipolar disorder remain unipolar). Patients with false unipolar have bipolar-like courses and some patients may be susceptible to an antidepressant-related switch to mania (Goodwin & Jamison, 2007, p. 14). Several identifying aspects of patients classified as “false unipolar” include early age at onset, a family history of BPD, atypical depressive features, depressive mixed state, and a large number of recurrences of major depressive episodes (Goodwin & Jamison, 2007, p. 17). In this section, I discuss studies assessing these aspects. As there are multiple publications from the same longitudinal dataset (Benazzi, 2007; Akiskal & Benazzi, 2006; Akiskal & Benazzi, 2005; Benazzi, 2003; Benazzi, 2000), these findings are described as a group.

Akiskal and Benazzi assessed 650 consecutively evaluated outpatients diagnosed with DSM-IV major depression. In their study, the DSM-IV criteria were modified to
two days for hypomania and subjects were rediagnosed using these modified criteria. There were 389 outpatients with BP-II ($M \pm SD$ age = 41.3 ± 12.9) and 261 outpatients with MDD ($M \pm SD$ age = 46.8 ± 14.8). Age of onset was defined as the age at which the patient recalls having his or her first major depressive episode (MDE); information regarding age of onset of hypomania is not considered as reliable, as research indicates patients with depression are not good at recalling earlier episodes of hypomania (Akiskal & Benazzi, 2006). A depressive mixed state was defined as experiencing three hypomaniac symptoms during a MDE. Atypical depressive features were defined using DSM-IV criteria.

Findings were: (1) age at onset of first MDE episode was significantly lower in the group with BP-II ($M \pm SD$ age = 22.8 ± 10.6) than in the group with MDD ($M \pm SD$ age = 31.8 ± 13.8); (2) a higher family history of BPD (BP-I and BP-II) was seen in the BP-II group (45%) than in the MDD group (15%); (3) patients with MDD and a family history of BPD were significantly younger, had a lower age of onset, more frequent episodes of depressive mixed states, and more atypical features compared to patients with MDD without a family history of BPD; (4) patients with MDD with a family history of BPD had similar ages of onset and similar rates of episodes of depressive mixed states as patients with BP-II. However, patients with BP-II had higher recurrence rates than patients with MDD with a family history of BPD; (5) patients with BP-II had more depressive mixed states than patients with MDD; (6) BP-II group was significantly more likely to have five or more recurrences of major depressive episodes (79%) than the MDD group (58%); (7) Atypical features were significantly more common in patients with BP-II (45%) than in patients with unipolar depression (25%), indicating that
depression with atypical depressive features was nearly two times more likely to occur in BP-II depression than in unipolar depression. This atypical depression group had a younger age at onset and higher rate of BP-II and depressive mixed states than the non-atypical depression group. The atypical depression group also had a higher family history of BPD, suggesting atypical depression may be a marker of BP-II. Leaden paralysis and hypersomnia were the atypical depressive symptoms most strongly associated with a family history of BPD. Depressive mixed states, BP-II and a family history of BPD were the strongest predictors of atypical depression; (9) hypomania scores were distributed normally and not bimodally. This normal distribution supports the idea of continuity, as there should be no symptom overlap between distinct disorders. Based on these cumulative findings, Akiskal and Benazzi suggest that highly recurrent unipolar disorder and BP-II lie on the same spectrum. They further suggest that atypical depression may be a “bridge” between unipolar depression and BP-II (Akiskal & Benazzi, 2005).

These findings indicate that early age at onset, a family history of BPD, atypical depressive features, depressive mixed states, and a large number of recurrences of major depressive episodes may provide clinical utility, as they can be used to predict which children will subsequently convert from unipolar to bipolar. As the findings reported in this section are from the same dataset, further studies using a different data set are needed to replicate the findings. Next, I discuss studies that assess prodromal symptoms of BPD in those at familial high risk for BPD and adults with BPD.
Prodromal Symptoms of Bipolar Disorder

Prodrome refers to the early symptoms indicative of the onset of an attack or a disease. Fava (1999) defines the prodromal phase as a “time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness” (p. 48). For example, an acute upper respiratory tract infection can have a short prodromal phase whereas viral hepatitis can have a long prodromal phase (Fava, 1999). Knowledge of prodromal symptoms can be helpful for clinicians and physicians in early detection of BPSD. In this section, I review studies assessing prodromal symptoms in familial high-risk youth and in adults with BPD.

Prodromal symptoms in familial high risk youth. Various studies have assessed prodromal symptoms and risk factors for childhood-onset BPD in high-risk youth (Chang, Steiner & Ketter, 2000; Shaw, Egeland, Endicott, Allen, & Hostetter, 2005). Chang, Steiner and Ketter (2000) assessed prodromal symptoms in 60 children ($M \pm SD$ age = 11.1 ± 3.5) from 37 families having at least one parent with BPD (BP-I, BP-II). Mean age of onset for bipolar symptoms was 14.8 years in their parents. Half of the parents had their onset of bipolar symptoms prior to age 15. Parents who had BPD and childhood attention deficit hyperactivity disorder (ADHD) showed, on average, an earlier age at onset for bipolar symptoms ($M = 11.3$ years) compared to the parents who had BPD but no childhood ADHD ($M = 15.6$ years). Of the 60 children, 15% were diagnosed with BPD; their mean age at onset for bipolar symptoms was 10.9 years. Over half (55%) had an Axis I disorder (28%, ADHD; 15%, MDD or DD; 15%, BPSD; 10%, oppositional defiant disorder [ODD]; 3%, obsessive compulsive disorder [OCD]; 3%, tic disorder; 5%, other anxiety disorders (separation anxiety disorder, generalized anxiety
disorder [GAD] and social phobia). Authors note that some children had more than one diagnosis. More children with BPD (56%) than children without BPD (17%) had a parent with BP-I or BP-II and a history of childhood ADHD. Offspring with bilineal risk (one parent with BP-I or BP-II and the other parent with BP-I, BP-II, or major depression) showed increased severity of depressed and irritable mood, as well as more problems with mood regulation (lack of mood reactivity and rejection sensitivity). Classic manic symptoms including grandiosity, euphoric mood or decreased sleep were not associated with offspring with either bilineal risk or offspring with unilineal risk (one parent with BP-I or BP-II, and other without mood disorder). This preliminary study (Chang, Steiner & Ketter, 2000) is not able to report on how many of those children with irritable and depressed mood and mood regulation dysfunction later developed BPD. However, Chang and colleagues are still following this cohort. Over time it is possible these symptoms may become evidence of prodromal symptoms of BPD, or they may merely be false positive symptoms (Chang, Steiner & Ketter, 2000).

In a 10-year prospective study by Shaw, Egeland, Endicott, Allen, and Hostetter (2005), prodromal features of BPD were assessed in offspring of BP-I probands ($n = 110$; 14 families) and compared to a matched control sample ($n = 112$; 13 families). All subjects were Amish and the mean age of sample was $17+\text{ years}$ ($SD = 7.3$ years reported in Egeland, Shaw, Endicott, Pauls, Allen, Hostetter & Sussex, 2003). Compared to offspring of control probands, bipolar offspring more frequently manifested the following thirteen features: anxious and worried; inattention and distractibility in school; easily excited; hyper-alert; mood changes and mood lability; role impairment in school; somatic complaints; stubbornness; high energy; decreased need for sleep; problems with thinking
and concentration; and excessive and loud talking. The researchers do not report clearly how many offspring met criteria for BPD. Carlson (2005) criticized this lack of bipolar diagnosis in offspring and the unconventional assessment procedures employed by Shaw and colleagues. She noted considering the family risk, 5 to 13 bipolar offspring should have developed BPD in this study. Although this study was prospective and longitudinal in design, it failed to report rates of BPD and thus, did not confirm whether the features common in bipolar offspring are prodromal symptoms of BPD.

Overall, these studies indicate: (1) 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. Further, these children with mood dysregulation may respond differently to external stressors (Chang, Steiner & Ketter, 2000). Moreover, if these children at-risk are treated with antidepressants and/or stimulants, these medications can trigger or worsen childhood mania (Geller et al., 1992). (2) Half of the parents with BPD had offspring with psychiatric conditions. Therefore, clinicians need to be aware of the family atmosphere and the influence of psychosocial stressors on the course of disorder for children as well as their parents with BPD (Chang, Steiner & Ketter, 2000). (3) The mean age of onset for bipolar symptoms in parents was 14.8 years, and 10.9 years in their offspring. This highlights the importance for clinicians and physicians to be cognizant of prodromal symptoms in bipolar offspring.

_Prodromal symptoms in adult populations with BPD._ Fava (1999) reviewed several studies assessing prodromal symptoms in bipolar and unipolar adult populations. He did not report exactly how many studies he reviewed, nor did he conduct a thorough meta-analysis. Still, his review provided some interesting findings. Mania had rapid
onset compared to either bipolar depression or unipolar depression. Bipolar depression had rapid onset compared to unipolar depression. Increased activity, elevated mood and decreased need for sleep were more likely prodromal symptoms for mania, while depressed mood, loss of energy and difficulty in concentration were more likely to be prodromal symptoms for bipolar depression. Further, prodromal symptoms preceding each episode were consistent for each individual across episodes, and some prodromal symptoms persisted as residual symptoms. Finally, atypical depression was associated with BPD.

In a systematic review of eight studies assessing prodromal symptoms in bipolar depression and 11 studies assessing prodromal symptoms in mania, prodromes of mania were more frequently identified than prodromes of depression (Jackson, Cavanagh & Scott, 2003). In these studies, the median prevalence of early symptoms for bipolar depression were: mood change (48%), psychomotor change (41%), increased anxiety (36%), appetite change (36%), suicidality (26%), disturbance (24%), and other symptoms (22%). The median prevalence of early symptoms for mania was: sleep disturbance (77%), psychotic symptoms (47%), mood change (43%), psychomotor symptoms (34%), other symptoms (30%), appetite change (20%), and increased anxiety (16%). Duration of prodrome was defined as the interval from which the first symptom was recognized to onset of the episode. The mean duration of manic prodromes was longer (range of 1 to 120 days with mean duration of 21-29 days) than depressive prodromes (range of 2 to 365 days with mean duration of 11-19 days). The authors speculated this may be because manic features are easier to recognize, as they differ from day-to-day experiences. Thus, this longer duration and manic prodromes may be an artifact of early detection, while
depressive features may get detected once they become more severe or persistent. Less severe symptoms may not influence behavior substantially and therefore a delay in recognizing symptoms can “shorten” the duration of a depressive prodrome.

Keitner, Solomon, Ryan, Miller, Mallinger, Kupfer and Frank (1996) retrospectively assessed prodromal symptoms in 74 patients with BP-I ($M \pm SD$ age = 42 ± 12) by using a semi-structured interview. Results indicated that prodromal symptoms for mania were highest for cognitive symptoms (35%; increased confidence and lack of concentration), followed by mood (15%; feeling high, irritability), behavioral (22%; more talkative, more aggressive), neurovegetative (22%; decreased sleep, more energy), social (1%; talking more to others), and other (5%). Cognitive symptoms (47%; poor concentration, inability to make decisions), mood (27%; crying, irritable and angry), behavioral (15%; quiet and withdrawn, self-neglect), neurovegetative (5%; poor sleep, loss of appetite and energy), social (1%; withdrawal from friends), and other symptoms (5%) were mostly likely to be prodromal symptoms for bipolar depression.

These studies indicate: (1) Sleep disturbance (median prevalence: 77%) was the most robust predictor of mania, whereas mood change (median prevalence: 48%) was the most robust predictor for bipolar depression. (2) The highest number of patients reported cognitive prodromal symptoms for mania and bipolar depression. Cognitive symptoms for mania included increased confidence and inability to concentrate. Cognitive symptoms for bipolar depression include poor concentration and inability to make decisions. Inability to concentrate appears to be a common prodromal symptom for mania and bipolar depression and therefore may need to be assessed in the context of other symptoms. (3) While familial high risk youth studies show increased severity of
depressed and irritable mood and problems with mood regulation as prodromes for mania, studies in adults with BP differ, showing increased activity, elevated mood, and decreased need for sleep as main prodromal symptoms. It is possible the differences between these two age groups occur because youth studies examined a high-risk population whereas adult studies assessed a bipolar sample. If these differences in manifestations are real and not because of sample differences, it would be interesting to assess whether the prodromal symptoms in youth differ due to developmental reasons. A longitudinal study assessing children with prodromal symptoms of mania who develop BPD is needed to compare prodromal symptoms of mania in the two age groups. (4) In adults with BPD, the characteristic prodrome for bipolar depression is depressed mood, loss of energy and difficulty in concentration. As no studies assess prodromes for bipolar depression in youth, comparisons between the two age groups cannot be made. Next, I review genetic studies that show a link between BPD and major depression.

Genetic Studies

Family studies demonstrate a genetic relationship between BPD and major depression. In addition, family, twin and adoption studies demonstrate the influence of genetic transmission in BPD and MDD (Goodwin & Jamison, 2007, pp. 414-422).

Family studies. Goodwin and Jamison (2007) estimated the genetic contribution of affective illness by analyzing family studies conducted after 1960. Studies prior to 1960 only assessed risk for BPD, whereas studies after 1960s assessed the independent morbid risk for BPD, for major depression and for schizoaffective disorder (SA) (p. 415). The lifetime prevalence rate in first-degree relatives of patients with BP-I were 5.2 % for BP-I, 3.8% for BP-II, 0.6% SA and 16.6% for MDD. For patients with BP-II, rates in
first degree relatives were 2.1% for BP-I, 6.5% for BP-II, 0.6% for SA and 21.6% for MDD. For patients with MDD, rates in first degree relatives were 0.8% for BP-I, 2.4% for BP-II, 0.5% SA, and 20.5% for MDD. However, the lifetime prevalence rate in first-degree relatives of patients with early-onset recurrent depression was 4.0-5.0% for early-onset recurrent major depression. The lifetime prevalence rate in first degree relatives of control probands was 0.1% for BP-I, 0.9% for BP-II, 0.3% SA and 7.3% for MDD. These results suggest a significant genetic contribution of BP-I, BP-II, MDD, SA, and early-onset recurrent major depression in first degree relatives of patients with BP-I, BP-II and MDD.

*Twin studies.* Goodwin and Jamison (2007) estimated concordance rates using the weighted mean of twin studies (p. 420). A concordance rate is the chance a person will develop a disorder if their twin has the disorder, where results are reported in percentages. 100% means perfect concordance and 0% means no concordance. The concordance rates for BP-I are 59% for Monozygotic (MZ), 10% for Dizygotic (DZ). The concordance rates for BP-II are 78% for MZ and 31% for DZ. The concordance rates for MDD are 34% for MZ and 26% for DZ. Similar to family studies, these results suggest a significant genetic contribution to BPD and MDD.

*Adoption studies.* Goodwin and Jamison (2007) evaluated four adoption studies (p. 421). The biological parents of adoptees with BPD had a 31% rate of affective disorders compared to a 12% rate in adopted parents of those adoptees. In control adoptees, there was a 2% rate in biological parent, and a 10% rate in the parents of polio probands (control group). This supports the genetic vulnerability for affective disorder in biological families of patients with BPD.
Family studies suggest a genetic relationship between BPD and major depression. Family, twin and adoption studies indicate that BPD, MDD and recurrent major depression have significant genetic contributions. If vulnerability for these disorders exists in an individual, environmental factors may play a role in onset of the disorder. Next, I discuss environmental factors that may act as precipitants of episodes.

Precipitants

Life events. Goodwin and Jamison (2007) reviewed fourteen studies that examined the influence of stressful life events on the onset of manic episodes in patients with BPD (p. 138). Their review concluded that more stressful events were seen prior to manic episodes compared to control groups. Further, more stress was more often associated with earlier rather than later episodes of mania. In addition, Goodwin and Jamison (2007) reported stressful life events may cause a loss of sleep, which in turn can trigger an onset of mania (p. 138). It is possible that stressful life events may trigger an episode of mania in patients diagnosed with unipolar depression who have a vulnerability to develop BPD.

Family atmosphere. Geller and colleagues (2001) found lower maternal warmth to be a predictor of mania. Asarnow and colleagues (1993) examined the association between one-year post hospitalization outcome with expressed emotion (EE; critical and hostile family environment) in 26 children (age 7 to 14 years) with depressive disorders and their parents. They found: (1) children with high EE were more likely to have a persistent mood disorder; (2) children with low EE showed higher rates of recovery. Thus, it is possible that a critical and hostile family environment may trigger an episode
of mania in patients diagnosed with unipolar depression who have a vulnerability to
develop BPD. To date no studies have assessed the influence of family environment on
unipolar patients who subsequently develop BPD.

Summary

Epidemiological studies assessing the lifetime prevalence rates for BPD in
children are lacking. The lifetime prevalence rates for BPSD in adolescent and adult
populations range from 6.4 to 6.7%. Retrospective adult studies indicate that BPD with a
prepubertal or adolescent onset is common. Earlier age of onset is associated with a more
pernicious course. Even though symptoms manifest at a younger age, accurate diagnosis
and treatment are delayed by many years due to frequent misdiagnosis or a delay in
receiving appropriate treatment. This can impair one’s individual and family life and
cause hardships. A majority of respondents experienced impairing symptoms prior to
diagnosis. Self-reported misdiagnosis of unipolar depression was common. This can be
a problem, as treatment with an inappropriate medication (e.g., stimulants or SSRIs) may
trigger mania (Geller et al., 1992). The rate of conversion from an initial unipolar to
subsequent BPD ranges from 7% to 50% in child, adolescent and adult populations,
indicating low diagnostic stability for MDD (Strober & Carlson, 1982; Geller, Fox &
Clark, 1994; Geller, Zimerman, Williams, Bolhofner and Craney, 2001; Akiskal et al.,
1995; Angst, Sellaro, Stassen & Gamma, 2005; Goldberg, Harrow & Whiteside, 2001).

Adult patients who are depressed with psychotic features are more likely to
experience mania or hypomania at follow-up. Further, in adult populations, a positive
family history of mania was found to increase the rate of conversion from unipolar to
BPD three-fold. Adult patients with more than six depressive episodes were three times
more likely to convert to BPD. A family history of BPD, rapid symptom onset, psychomotor retardation, mood congruent psychosis and a pharmacologically induced mania predicted onset of mania in children and adolescents diagnosed with MDD. In one study, atypical depressive features and the use of tricyclic antidepressants did not predict conversion to BPD (Geller, Fox & Clark, 1994). Depression with atypical depressive features is two times more likely to occur in BP-II depression than in unipolar depression (Akiskal & Benazzi, 2006).

Studies show several aspects (age at onset, atypical depressive features, mixed state, recurrence, a family history of BPD) differ between unipolar disorder and BPD and these aspects can be used by clinicians to predict which patients with unipolar disorder will subsequently convert to BPD. Age of onset is younger in patients with BPD than in patients with unipolar disorder. Early onset has a poorer prognosis than later onset and childhood-onset is often associated with a delay in diagnosing BPD and a delay in receiving required treatment. A greater incidence of a family history of BPD is seen in patients with BPD than in patients with MDD. Patients with MDD and a family history of BPD often show a younger age of onset and more depressive mixed states than patients with MDD without a family history of BPD. A family history of mania in parents and grandparents predicted a BP-I outcome for patients. Prodromal symptoms differ in high-risk youth populations compared to populations of adults with BPD. Familial high-risk youth show increased severity of depressed and irritable mood and problems with mood regulation. Adult studies indicate sleep disturbance is a robust predictor of mania. Also, cognitive prodromal symptoms predict mania in adult populations. Genetic studies indicate a link between unipolar disorder and BPD. There
is significant genetic contribution to the development of BPD and MDD. Precipitants such as stressful life events and low levels of maternal warmth can trigger mania in individuals vulnerable to developing BPD.

Purpose of the Present Study

No studies have assessed the rates of conversion to BPSD in children with DSD + TMS. As mentioned earlier, TMS are defined as manic-like symptoms of insufficient duration or number to warrant a diagnosis of BPSD. Studying rates of conversion from DSD to BPSD allows for the assessment of risk factors that can predict bipolarity in this sample. The aim of the present study was to provide 18-month longitudinal follow-up data of children diagnosed with DSD + TMS. This study compared Children’s Global Assessment Scale (C-GAS) scores for the children with DSD + TMS to the children with DSD and to the children with BPSD at baseline (Time 1). Further, this study assessed how many children with DSD + TMS converted to BPSD on follow-up in comparison with DSD and which predictors [prodromal manic symptoms, prodromal duration, the level of global impairment, life events, a critical and hostile family environment, family history (biological parents and second degree relatives) of major affective disorder (BPD, depression, schizoaffective disorder), current levels of parental depression and mania] predicted bipolarity.

Primary hypotheses included:

1. At Time 1, children with DSD + TMS will have lower C-GAS scores than children with DSD but higher scores than children with BPSD.

2. Children with DSD + TMS at Time 1 will convert to BPSD at follow-up at a higher rate than children with DSD at Time 1.
3. Conversion rates will not differ for DSD + TMS participants in the immediate treatment (IMM) and a one-year wait-list control (WLC) group at Time 3.

4. Children with DSD + TMS at Time 1 who convert to BPSD at follow-up (converted group) will have greater impairment than those who do not convert (i.e., non-converted group) on the following Time 1 variables:
   a) Clinical presentation;
   b) Family environment;
   c) Family history.

The following secondary hypotheses were conducted to see which, if any, components of the composite variables differed:

The converted group will differ from the non-converted group on the following Time 1 variables:

1. Clinical presentation:
   a. Greater severity of prodromal manic symptoms;
   b. Longer duration of prodromes;
   c. Lower C-GAS scores;

2. Family environment:
   a. Greater number of life events;
   b. More critical and hostile family environment;

3. Family history:
   a. Higher rates of diagnosis and symptoms of BPD for both parents;
   b. Higher rates of diagnosis and symptoms of BPD in second degree relatives;
c. Higher rates of diagnosis and symptoms of a loaded family history (i.e., parents and second degree relatives’) of major affective disorder (i.e., BPD, major depression, and schizoaffective disorder);

d. Higher mood severity in the parent as measured by Mood Severity Index.
Chapter 2: Method

Participants

One hundred and sixty-five prepubertal children aged between 8 and 11 at Time 1 ($M = 9.9, SD = 1.3$) with a mood diagnosis participated in the MFPG (Multi-family Psychoeducation Group) treatment study. 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) participated in the study. The mean age of participating parents was 40.8 ($SD = 7.8$) at Time 1.

For each family set (consisting of 15 families), seven families were randomized into immediate treatment (IMM) and eight were randomized into a one-year wait-list control (WLC) condition. There were a total of 11 family sets. One family was erroneously assigned to IMM who should have been in WLC. This resulted in 78 families participating in the IMM group, and 87 in the WLC group. All families received treatment-as-usual (TAU) throughout the study.

Procedure

The participants were recruited via a variety of methods, including: communication by letter with an established referral network of mental health professionals; presentations to local professional and community-based groups; posters in public libraries; word-of-mouth; and by local media (newspaper, radio and television)
feature stories describing the study and recruitment information. Special efforts were taken to facilitate recruitment of minority participants by ongoing contact with urban minority cultural organizations and schools. At Time 1 all children received study diagnoses of BPSD or DSD then they were randomized to an immediate treatment group (IMM) or a one year wait-list control group (WLC). Everyone was encouraged to continue treatment-as-usual (TAU) throughout the study duration. Assessments were conducted at four time points, Time 1, 6 months (Time 2), 12 months (Time 3) and 18 months (Time 4). The IMM group participated in MFPG after their Time 1 assessment and before their Time 2 assessment. The WLC group participated in MFPG after their Time 3 assessment and before their Time 4 assessment. A summary of the study schedule and sample size at each time point is shown in Table 2.1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMM</td>
<td>N = 165</td>
<td>N = 144</td>
<td>N = 122</td>
<td>N = 109</td>
</tr>
<tr>
<td></td>
<td>Pre-MFPG</td>
<td>Post-MFPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 78</td>
<td>n = 70</td>
<td>n = 61</td>
<td>n = 56</td>
</tr>
<tr>
<td>WLC</td>
<td></td>
<td></td>
<td>Pre-MFPG</td>
<td>Post-MFPG</td>
</tr>
<tr>
<td></td>
<td>n = 87</td>
<td>n = 74</td>
<td>n = 61</td>
<td>n = 53</td>
</tr>
</tbody>
</table>

*Note: IMM = immediate treatment group; WLC = wait-list control group. MFPG = Multi-family Psychoeducation Group.*

Table 2.1 MFPG Study Schedule and Sample Size at Each Time Point

At Time 1 there were 115 participants in bipolar spectrum disorder (BPSD) group, 37 in depressive spectrum disorder with transient manic symptoms (DSD + TMS)
group, and 13 in depressive spectrum disorder without transient manic symptoms (DSD) group (see Table 2.2 for diagnostic criteria for Bipolar Disorder and TMS). The three groups did not differ significantly on any of the demographic characteristics at Time 1. There were 17 drop-outs in the DSD + TMS and DSD groups by Time 4 (see Figure 2.1). For hypothesis two, I compared 25 participants from DSD + TMS Time 1 group with 8 from DSD Time 1 group. For hypothesis three I compared participants (DSD + TMS) in the IMM \( (n = 12) \) with WLC \( (n = 15) \) group at Time 3 (2 Time 3 participants from WLC subsequently dropped out by Time 4). For hypothesis four and supplementary analyses I compared 12 participants from the converted group (participants with DSD + TMS at Time 1 who converted to BPSD at follow-up) with 13 participants from the non-converted group (participants with DSD + TMS at Time 1 who did not convert to BPSD at follow-up).

Figure 2.1. Participants Flow Diagram for DSD + TMS and DSD Groups
### Diagnostic Criteria Based on the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR (American Psychiatric Association, 2000) and MFPG Study

#### Bipolar I Disorder (DSM-IV-TR)
- Presence of a Manic Episode and no history of Major Depressive Episode (MDE)
- Manic Episode not better accounted for by Schizoaffective Disorder and not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified (NOS)

#### Bipolar II Disorder (DSM-IV-TR)
- Presence or history of one or more Major Depressive Episode (MDE)
- Presence or history of at least one Hypomanic Episode
- No history of a Manic Episode or a Mixed Episode
- Mood symptoms not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS

#### Bipolar Disorder, Not Otherwise Specified (MFPG Study)
- Elated mood plus 2 of the following symptoms:
  - inflated self-esteem/grandiosity, decreased need for sleep, more talkative/pressured speech, flight of ideas/racing thoughts, distractibility, increase in goal directed activity/psychomotor agitations, poor judgment/involvement in risky behaviors
- Symptoms must be present for a total of at least 4 hours within a 24-hour period
- Individual must have had at least 4 episodes of 4 hours duration or a total of 4 days of above-noted symptom intensity in their lifetime
- Evidence of functional impairment

#### Transient Manic Symptoms (TMS) (MFPG Study)
- Any one of the following symptoms:
  - 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 consequences
- These mood symptoms can be differentiated from Attention Deficit/Hyperactivity Disorder symptoms with reasonable certainty
- Frequency/intensity/duration is characterized by:
  - one to three manic-like episodes of moderate to severe intensity lasting 4 or more hours
  - two or more brief episodes of 2 to 4 hours duration
- Evidence of functional impairment

Table 2.2 Diagnostic Criteria for Bipolar Disorder and Transient Manic Symptoms
Family Intervention

The IMM group received MFPG after their Time 1 assessment and the WLC group after their Time 3 assessment. MFPG involves three primary components: psychoeducation, social support and skills development. Eight weekly psychoeducation sessions of 90-minute duration are conducted with families. Each session is highly structured and includes specific content to be taught and skills to be practiced. Sessions begin and end with parents and children together. At the beginning of each session, family members review and ask questions on previous material. Then children and parents break up into two groups. The goal and objectives of parent and child sessions are related, however separate groups allow content to be presented in an age appropriate manner. Each session ends with children joining the parents’ group. This provides an opportunity for children to review with their parents what they did during the session and to review the family project for the next week. The parent group was led by a doctoral level clinician and the child group was led by a post-doctoral fellow or advanced graduate student in clinical child psychology. A clinical child psychology graduate student assisted as a co-leader for behavioral management. Detailed descriptions of session content appear elsewhere (Fristad & Goldberg-Arnold 2003; Goldberg-Arnold & Fristad 2003).

Instruments

Socio-demographic information, including age, sex, ethnicity, income level, family structure, and the parent’s relationship with the child (e.g., biological parent, stepparent, adopted parent) was collected at Time 1. In addition, a variety of measures described below assessed clinical presentation, family environment and family history.
In addition a diagnostic interview was conducted at Time 1 to determine the presence of DSM-IV diagnoses in the children and a cognitive screen was administered to rule out intellectual deficiency.

The *Children’s Interview for Psychiatric Syndromes – Child and Parent Form* (ChIPS, P-ChIPS; Weller, Weller, Rooney, & Fristad, 1999a; Weller, Weller, Rooney, & Fristad, 1999b) is a structured psychiatric interview that assesses psychopathology according to DSM-IV criteria for children and adolescents aged six to 18 years. ChIPS and P-ChIPS assess 20 behavioral, anxiety, mood, and other syndromes as well as psychosocial stressors, including abuse and neglect. Symptoms are assessed using a yes/no question format. Its reliability and validity as a diagnostic instrument in clinical research has been demonstrated in child and adolescent samples, age six to 18 years (Weller, Weller, Fristad, Rooney, & Schecter, 2000). This diagnostic interview was conducted at the Time 1 and Time 3 assessment to determine diagnostic status of the participants.

The *Kaufman Brief Intelligence Test* (K-BIT; Kaufman & Kaufman, 1990) assesses intelligence in persons ages four through 90, and consists of three subtests, two which provide verbal intelligence through vocabulary and naming, and one which assesses nonverbal intelligence through various visuo-spatial exercises (Kaufman & Kaufman, 1990). The K-BIT has shown to be a reliable and valid screening measure of intellectual ability (Naugle, Chelune, & Tucker, 1993). The K-BIT was administered to each child upon study entry to estimate IQ.
Clinical Presentation

The Mania Rating Scale (MRS; Young, Biggs, Ziegler, & Meyer, 1978) is an 11 item clinical rating scale for manic symptoms. Items are rated either from 0 to 4 (7 items) or from 0 to 8 (4 items), depending on item weighting, in the direction of increasing severity. Total scores can range from 0 (no symptoms) to 60 (severe symptoms). The MRS has shown good psychometric properties (Fristad, Weller, & Weller, 1992; Fristad, Weller, & Weller, 1995; Youngstrom, Danielson, Findling, Gracious, & Calabrese, 2002). In this study, the MRS provided information on the severity of prodromal manic symptoms in children. The MRS was administered to each parent (about the child) and child at every assessment. The Time 1 parent MRS was used to calculate a composite clinical presentation variable for hypothesis four and was an outcome variable in a secondary analysis. In addition, diagnostic status of the participants at Time 2 and Time 4 was determined using MRS.

The Children’s Depression Rating Scale - Revised (CDRS-R; Poznanski et al., 1984) is a clinician-rated severity scale based on the report of parent or child for depression in children age six to 17. The CDRS-R has 21 items, each rated on a 1-5 or 1-7 point scale in the direction of increasing severity. Scores can range from 17 to 113. The CDRS-R shows adequate inter-rater reliability ($r = 0.86$) and test-retest reliability ($r = 0.81$) over a 4-week interval (Poznanski et al., 1984). This measure was administered to each parent (about the child) and child at every assessment. The parent CDRS-R was used to assess diagnostic status of the participants at Time 2 and Time 4.

The Children's Global Assessment Scale (C-GAS) is a clinician rating of a child’s global functioning ranging from one (indicating a child with severe impaired functioning)
to 100 (indicating a child with superior functioning) (Shaffer et al., 1983). C-GAS scores are assigned based on the clinician’s assessment of the child’s functioning at home, school, and with peers. Two clinical psychologists separately read reports that summarized each assessment, then held a consensus conference to arrive at one C-GAS score. The C-GAS was completed at each time point to provide a severity of impairment index. In calculating the weighted kappa statistic, a weight matrix assigned each combination of ratings (x1 = rater 1, x2 = rater 2) with a weight, ranging from 1 = perfect match to 0 = no match. For the CGAS, if x1 and x2 were within 5 points of each other, the weight was 1 and considered a perfect match. Beyond 5 points, the weight went downwards as x1 and x2’s ratings grew further apart. Using this method, the inter-rater reliability between the two raters in the MFPG study was substantial ($\kappa = 0.68$, $CI_{95} = 0.59, 0.78$). Baseline C-GAS scores were used to calculate a composite clinical presentation variable for hypothesis four and was an outcome variable for hypothesis one and a secondary analysis.

*Duration of prodromes.* Age of onset for prodromal symptoms was recorded in years and months. Prodromal symptoms were defined as symptoms interfering in functioning but not at a diagnostic level. When there was absence of prodromal symptoms, a coding of 0 was recorded. Duration of prodromes was calculated by subtracting age of onset for prodromal symptoms from age of onset for the first mood episode. The duration of prodromes did not distinguish between manic or depressive symptoms as the age of onset of prodromal symptoms and age of onset of the first mood episode was noted for affective changes and was not specific to mania or depression.
Baseline duration of prodromes was used to calculate composite clinical presentation variable for hypothesis four and as an outcome variable for a secondary analysis.

*Composite clinical presentation variable.* A composite variable for clinical presentation was created by calculating dummy codes for duration of prodromes, number of manic symptoms and C-GAS. Dummy codes were assigned after calculating Time 1 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; a code of 3 was recorded for C-GAS scores in the fourth quartile. Therefore, the dummy coded C-GAS ranged from 0 to 3. Dummy coding for duration of prodromes and number of manic symptoms was done similarly. Finally a composite score for clinical presentation was calculated by summing the three dummy coded variables. Thus, composite score can range from 0 to 9, with higher numbers indicating greater impairment.

*Family Environment*

The *Coddington Life Events Scale for Children* (LES; Coddington, 1983) assesses parental report of 36 recent stressors in the child’s life. Life events are assessed using a yes/no question format. Each stressor was weighted based on the amount of stressors experienced (weight range from 25 to 91) (Coddington, 1983). A total score can be derived to quantify the amount of stress the child has experienced. Score can range from zero to 1,794. Test-retest reliability and parent-child agreement are adequate (Coddington, 1983). This scale was administered at Time 1 to document stressful life
events in the family prior to study entry. The Time 1 LES score was used to calculate the composite family environment variable for hypothesis four and as an outcome variable for supplementary analyses. The LES score was missing for one participant.

The *Expressed Emotion Adjective Checklist* (EEAC; Friedmann & Goldstein, 1993) lists 20 positive and negative descriptors of criticism and emotional over-involvement. Expressed emotion refers to an intrusive and critical interactive style, which reflects the quality of family environment. Items are administered twice, first to record the informant’s behavior toward a target person over three months, second to record the target person's behavior toward the informant over the same time period. The response ranges from 1 (never) to 8 (always) and the global score ranges from -140 to 140. A higher value indicates a less critical, intrusive style of interacting and a lower value indicates a more critical, intrusive style of interacting. Internal consistency is good for this instrument. Coefficient alphas for negative adjectives are 0.88 for a relative’s rating of personal behavior toward the patient and 0.92 for the patient’s behavior toward the relative. For positive adjectives the coefficient alpha is 0.91 for the relative’s rating of personal behavior toward the patient and 0.94 for the patient’s behavior toward the relative. If both parents reported hostile and critical environment, the lowest (i.e., worst) reported level was used for the analysis. This measure was administered at Time 1 to assess a critical and hostile family environment. The Time 1 EEAC score was used to calculate the composite family environment variable for hypothesis four and as an outcome variable for supplementary analyses.

**Composite family environment variable.** A composite family environment variable was created by calculating dummy codes for the LES and EEAC. Dummy
coding was done comparably to the clinical presentation dummy codes. Thus, a code of 0 was recorded for LES scores in the lowest quartile; a code of 1 was recorded for LES scores in the second quartile; a code of 2 was recorded for LES scores in the third quartile; a code of 3 was recorded for LES scores in the fourth quartile. Therefore, dummy coded LES scores ranged from zero to three. Dummy coding for the critical and hostile family environment variable was done similarly. Finally a composite score for family environment was calculated by summing these two dummy coded variables. The composite score had a possible range of 0 to 6 with higher number indicating greater impairment. The composite score was used as an outcome variable for hypothesis four. The composite score was missing for one participant due to the missing LES score.

**Family History Variables.**

The *Ohio State Adapted Family History – Research Diagnostic Criteria* (FH-RDC; Andreasen, Endicott, Spitzer & Winokur, 1977; Fristad, 1986) was used to collect Time 1 information concerning symptoms and diagnosis of a family history of 13 major psychiatric disorders (senile organic brain syndrome, alcoholism, drug use disorder, mania, depressive disorder, BPD – subjects meeting criteria for both manic disorder and depressive disorder, schizophrenia or schizoaffective disorders, antisocial personality disorder, somatization disorders, eating disorders, anxiety disorders, mental retardation, and other psychiatric disorders) or no known mental disorder in the first and second degree relatives of probands. The diagnostic reliability is good to excellent for high-threshold diagnosis (depression, alcoholism, drug abuse, antisocial personality), but not for other psychiatric disorders (Zimmerman, Coryell, Pföhl, & Stangl, 1988). For this study, four summary variables were created. This was done to: use all available
information; avoid giving higher scores to probands based on larger pedigrees; and give
greater weight to diagnoses than symptoms. A drawback of this summary variable
calculation is that two relatives with symptoms of a diagnosis are equated with one
relative having a diagnosis. The four summary variables were: (1) parental BPD scale:
the mean level of symptom and diagnosis of BPD for both parents was calculated with
the formula (mother’s bipolar score + father’s bipolar score/ number of parents with
FH-RDC information). The parental BPD scale score was used as an outcome variable
for supplementary hypotheses. This score could not be calculated for two participants as
they were both from adoptive families who did not have mental health history for the
birth parents; (2) second degree relatives’ BPD scale: the mean level of second degree
relatives with symptoms and diagnosis of BPD was calculated with the formula
[2*(number of maternal and paternal second degree relatives with diagnosis of BPD)
+ (number of maternal and paternal second degree relatives with symptoms of
BPD)/number of second degree relatives with FH-RDC information]. The second degree
relatives’ BPD scale score was used as an outcome variable for supplementary
hypotheses. This score could not be calculated for three participants (two from adoptive
family and one from stepfamily) who did not have mental health history for extended
families; (3) loaded family history BPD scale: the mean level of BPD in parents and
second degree relatives was calculated with the formula [(mother’s bipolar
score + father’s bipolar score) + 2*(number of maternal and paternal second degree
relatives with diagnosis of BPD) + (number of maternal and paternal second degree
relatives with symptoms of BPD)/(number of parents with FH-RDC information
+ number of second degree relatives with FH-RDC information)]. Summary scores were
missing for two participants due to the missing scores for parents. The loaded family history BPD scale score was used to calculate a composite family history variable for hypothesis four; (4) loaded family history major affective disorder scale: the mean level of major affective disorder (BPD, major depression and schizoaffective disorder) in parents and second degree relatives was calculated with the formula [(sum of mother’s and father’s score on BPD, depression and schizoaffective disorder) + 2*(sum of number of maternal and paternal second degree relatives with diagnosis of BPD, depression and schizoaffective disorder) + (sum of number of maternal and paternal second degree relatives with symptoms of BPD, depression and schizoaffective disorder)/ (number of parents with FH-RDC information + number of second degree relatives with FH-RDC information)]. The loaded family history major affective disorder scale score was used as an outcome variable for supplementary hypotheses. The information on family history of major affective disorder in parents and second degree relatives was missing for two participants as the information was missing for parents.

The Mood Severity Index (MSI) for parents was calculated using the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1967) and the Mania Rating Scale (MRS; Young, Biggs, Ziegler, & Meyer, 1978). The HAM-D is a 17-item scale that assesses depressive symptomatology in adults. The scores range from 0 to 50. The scale has high inter-rater reliability and adequate validity (Hedlund & Vieweg, 1979). The HAM-D was administered at Time 1 to assess current levels of depression in one or both parents. If both parents reported depression, the highest reported level was used for the analysis. The MRS was administered to parents at Time 1 to assess current levels of mania in one or both parents. If both parents reported mania, the highest reported level
was used for the analysis. An MSI score was calculated with the formula \((5/6 \times \text{MRS score}) + (11/17 \times \text{HAM-D score})\). This formula takes into consideration the higher number of items on the HAM-D and the higher total range on the MRS. The scores range from 0 (none) to 100 (severe). When MSI scores were available for both parents, the highest MSI score was used for the analysis. The MSI was calculated at Time 1 to assess mood severity in parents. The Time 1 MSI was used to calculate the composite family history variable for hypothesis four and as an outcome variable for supplementary analyses.

*Composite family history variable.* A composite family history variable was created by calculating dummy codes for FH-RDC and MSI. Dummy coding was done comparably to the clinical presentation dummy codes. Thus, a code of 0 was recorded for MSI scores in the lowest quartile; a code of 1 was recorded for MSI scores in the second quartile; a code of 2 was recorded for MSI scores in the third quartile; a code of 3 was recorded for MSI scores in the fourth quartile. Therefore, dummy coded MSI scores ranged from zero to three. Dummy coding for loaded family history BPD scale using FH-RDC was done similarly. Finally a composite score for family history variable was calculated by summing these two dummy coded variables. The composite score can range from 0 to 6 with higher numbers indicating greater impairment. The composite score was used as an outcome variable for hypothesis four. The composite scores were missing for two participants due to two missing scores on loaded family history BPD scale.
Service Utilization

At each assessment, a report was prepared by the interviewers summarizing their findings. This report was reviewed independently by two licensed psychologists experienced in childhood mood disorders. These two psychologists provided ratings of the child’s utilization of various services (medication, school, therapy and overall). Each service utilization score (i.e., for medication, therapy and school based services) ranged from one to five, with higher scores indicating better service utilization (see Table 2.3 for a copy of the Consensus Conference Utilization Scoring Guide).

<table>
<thead>
<tr>
<th>MFPG Consensus Conference Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td>• child has a prescribing physician</td>
</tr>
<tr>
<td>• relevant medications are prescribed by the physician and the child is monitored for mood symptoms</td>
</tr>
<tr>
<td>• relevant medications are prescribed by the physician and the child is monitored non-mood comorbid symptoms</td>
</tr>
<tr>
<td>• successful communication between the family and the prescribing physician</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
</tr>
<tr>
<td>• child has a therapist</td>
</tr>
<tr>
<td>• child and therapist have a positive relationship</td>
</tr>
<tr>
<td>• parents and therapist have a positive relationship</td>
</tr>
<tr>
<td>• relevant symptoms are targeted and addressed</td>
</tr>
<tr>
<td><strong>School</strong></td>
</tr>
<tr>
<td>• school knows the problems faced by the child, as evidenced by school services (if school-based problems are absent, child earns a point)</td>
</tr>
<tr>
<td>• cognitive issues are addressed at school (if cognitive issues are absent, child earns a point)</td>
</tr>
<tr>
<td>• social-emotional issues are addressed at school (if social-emotional issues are absent, child earns a point)</td>
</tr>
<tr>
<td>• appropriate placement based on level and type of care required</td>
</tr>
</tbody>
</table>

Table 2.3. MFPG Consensus Conference Utilization Scoring Guide
The average rating of these three categories were the Overall service utilization scores. If the two raters disagreed on assigned scores, the average of the two independently derived scores was used. Data were missing for one participant from the WLC group at Time 1. To understand the possible influence of treatment condition on conversion rates, change scores were calculated to determine differences in service utilization from Time 1 to Time 3 in the IMM and WLC groups. For example, change medication utilization service score = Time 3 medication service utilization score – Time 1 medication service utilization score. Similar change scores were calculated for school, therapy and overall service utilization.

Data Analyses

Missing data. Missing data at Time 1 were rare. When they occurred, they were managed as follows: (1) if a participant did not answer one question on a self report measure, the score was imputed for the missing answer using the mean response for that person; (2) if an entire measure or more than a quarter of the measure was missing for a participant, then it was treated as missing.

Drop outs. For hypothesis two, three, four and secondary hypotheses, analyses were conducted after excluding subjects who dropped out ($n = 12$) before the study ended. The robustness of findings from these analyses was tested by conducting intent to treat (ITT) analyses to account for study drop outs. Twelve subjects had their last observation (LOCF) carried forward to impute Time 4 missing data, which resulted in 37 participants for the DSD + TMS group and 13 for the DSD group.

Multiple comparisons. As these were exploratory hypotheses, corrections were not made for multiple comparisons.
Statistical procedures. Hypothesis testing utilized the following statistical procedures:

1. *At Time 1, children with DSD + TMS will have lower C-GAS scores than children with DSD but higher scores than children with BPSD.*

   A one-way ANOVA with diagnostic group (DSD, DSD + TMS 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. Tukey’s post-hoc analysis was conducted to complete pairwise comparisons (DSD + TMS versus DSD; DSD + TMS versus BPSD; DSD versus BPSD).

2. *Children with DSD + TMS at Time 1 will convert to BPSD at follow-up at a higher rate than children with DSD at Time 1.*

   A Fisher’s Exact Test was used to compare the proportion of conversion rates for each group.

3. *Conversion rates will not differ for participants (DSD + TMS) in the IMM and WLC group at Time 3*

   To examine the possible impact of treatment on rates of conversion, a Fisher’s Exact Test was used to compare the proportion of conversion rates from DSD + TMS at Time 1 to BPSD at 12 months for participants in the IMM and WLC groups.

4. *The converted group will have greater impairment than the non-converted group on the following Time 1 variables:*

   43
a) Clinical presentation

A two-sample t-test was conducted to assess whether the mean level of impairment in clinical presentation at Time 1 (as measured by the composite clinical presentation variable) differed between the two groups.

b) Family environment

A two-sample t-test was conducted to assess whether the mean level of impairment in family environment at Time 1 (as measured by the composite family environment variable) differed between the two groups.

c) Family history

A two-sample t-test was conducted to assess whether the mean level of impairment in family history at Time 1 (as measured by the composite family history variable) differed between the two groups.

Secondary analyses included:

The converted group will differ from the non-converted group on components of the composite variables:

1. Clinical presentation:
   a) Greater severity of prodromal manic symptoms

   A two-sample t-test was conducted to assess whether the average severity of prodromal manic symptoms differed between the two groups.

   b) Longer duration of prodromes

   A two-sample t-test was conducted to assess whether the mean duration of prodromes differed between the two groups.
c) **Lower C-GAS scores**

A two-sample t-test was conducted to assess whether the average C-GAS scores differed between the two groups.

2. **Family environment:**

a) **Greater number of life events**

A two-sample t-test was conducted to assess whether the average number of life events differed between the two groups.

b) **More critical and hostile family environment** (i.e., lower EEAC scores)

A two-sample t-test was conducted to assess whether the mean level of critical and hostile family environment differed between the two groups.

3. **Family history:**

a) **Higher scores on parental BPD scale**

A two-sample t-test was conducted to see whether the mean scores on the parental BPD scale differed between the two groups.

b) **Higher scores on second degree relatives’ BPD scale**

A two-sample t-test was conducted to see whether the mean scores on the second degree relatives’ BPD scale differed between the two groups.

c) **Higher scores on loaded family history major affective disorder scale**

A two-sample t-test was conducted to see whether the mean scores on the loaded family history major affective disorder scale differed between the two groups.

d) **Higher mood severity in the parent as measured by the MSI**

A two-sample t-test was conducted to assess whether the parents’ mean level of mood severity differed between the two groups.
**Power analyses.** Based on results from the above-described hypothesis testing, power analyses using Dean and Voss’ methodology (1999) was calculated to determine the sample sizes needed to test hypotheses one and four in future studies. The effect sizes (Cohen’s $d$, Cramer’s $V$ and partial eta squared) were calculated for all hypotheses to assess the strength of the relationship between two variables.
Chapter 3: Results

Descriptive Statistics

Demographics. One hundred and sixty-five prepubertal children aged 8 and 11 at Time 1 ($M \pm SD = 9.9 \pm 1.3$) with a mood diagnoses participated in the MFPG (Multi-family Psychoeducation Group) treatment study. A majority (73%) were male. The mean age of participating parents was 40.8 ($SD = 7.8$) at Time 1. The sample was primarily White (91%; 150 Caucasian, 11 African Americans, 3 Mixed and 1 Hispanic). Less than half (43%) of the children were from married biological parents households, 20% were from stepfamily households, 19% were from single-parent households, 7% were from adoptive parents households and 11% were from households with other family constellations. The median family income of the sample was between $40,000 and $59,000 per year and ranged from less than $20,000 to over $100,000. Participants were diagnosed with a comorbid behavioral disorder (97%) (e.g., ADHD, ODD) and/or a comorbid anxiety disorder (69%) (e.g., GAD, OCD). The children’s IQ ranged from 71 to 148 ($M \pm SD = 106.9 \pm 14.9$).

A majority (70%, $n = 115$) were diagnosed with BPSD, 22% ($n = 37$) with DSD + TMS and the remainder (8%, $n = 13$) with DSD. The three groups did not differ significantly on gender [$FET = 0.22, p = 0.88$]; parent’s age [$F (2, 161) = 0.24, p = 0.79$]; race, [$FET = 3.96, p = 0.73$]; family structure [$FET = 10.36, p = 0.77$]; family income
\[FET = 5.03, p = 0.91]\]; co-morbid behavior disorder \[FET = 1.74, p = 0.40]\]; co-morbid anxiety disorder \[FET = 0.11, p = 0.96]\); or IQ \[F (2, 156) = 2.39, p = 0.10]\] (see Table 3.1). In this age group males are common. A one-way ANOVA revealed that participants’ age differed marginally as a function of diagnostic status at Time 1 \[F (2, 162) = 2.56, p = 0.08]\); however, no specific Tukey’s post-hoc contrasts were significant.

<table>
<thead>
<tr>
<th>Characteristics at Time 1(^a)</th>
<th>BPSD (n = 115)</th>
<th>DSD + TMS (n = 37)</th>
<th>DSD (n = 13)</th>
<th>(p=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>83 (72%)</td>
<td>28 (76%)</td>
<td>10 (77%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Age in years</td>
<td>9.7 (1.3)</td>
<td>10.1 (1.3)</td>
<td>10.4 (1.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Parent’s age in years</td>
<td>39.8 (6.3)</td>
<td>40.9 (9.6)</td>
<td>37.8 (8.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>105 (91%)</td>
<td>33 (89%)</td>
<td>12 (92%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Non-white</td>
<td>10 (9%)</td>
<td>4 (11%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Family structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married bio parents</td>
<td>53 (46%)</td>
<td>14 (38%)</td>
<td>4 (31%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Step-family</td>
<td>25 (22%)</td>
<td>6 (16%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>Single parent</td>
<td>19 (16%)</td>
<td>8 (22%)</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td>Adoptive parents</td>
<td>8 (7%)</td>
<td>3 (8%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Foster family and other</td>
<td>10 (9%)</td>
<td>6 (16%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $40,000</td>
<td>34 (30%)</td>
<td>14 (38%)</td>
<td>6 (46%)</td>
<td>0.91</td>
</tr>
<tr>
<td>$40,000 – $80,000</td>
<td>41 (36%)</td>
<td>15 (40%)</td>
<td>3 (23%)</td>
<td></td>
</tr>
<tr>
<td>Greater than $80,000</td>
<td>40 (34%)</td>
<td>8 (22%)</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td>Co-morbid disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior disorders</td>
<td>112 (97%)</td>
<td>36 (97%)</td>
<td>12 (92%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>78 (68%)</td>
<td>26 (70%)</td>
<td>9 (69%)</td>
<td>0.96</td>
</tr>
<tr>
<td>IQ</td>
<td>106.0 (15.1)</td>
<td>112.2 (17.1)</td>
<td>109.3 (9.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

\(^a\)Values represent mean (\(SD\)) or frequency (%).

Table 3.1. Sample Characteristics of BPSD, DSD + TMS and DSD Subjects at Time 1
For hypothesis one, analyses were run on the entire sample \((N = 165)\). For hypotheses two, three, four and supplementary analyses, the subsample consisted of diagnostic status DSD + TMS and/or DSD identified at Time 1. In DSD + TMS and DSD groups there were 17 drop-outs by Time 4 (see Figure. 2.1). For hypothesis two, the sample was determined by diagnostic status identified at Time 1 (DSD + TMS, \(n = 25\); DSD, \(n = 8\)). Hypothesis three utilized the DSD + TMS subsample \((n = 27)\) at Time 3. For hypothesis four and secondary analyses, the converted group (i.e., DSD + TMS who converted to BPSD by Time 4; \(n = 12\)) was compared to the non-converted group (i.e., DSD + TMS who did not convert to BPSD by Time 4; \(n = 13\)).

**Hypotheses Testing**

As these are exploratory hypotheses, no corrections were made for multiple comparisons.

**Hypothesis one: At Time 1, children with DSD + TMS \((n = 37)\) will have lower C-GAS scores than children with DSD \((n = 13)\) but higher scores than children with BPSD \((n = 115)\).** A one-way ANOVA revealed the three diagnostic groups (DSD, DSD + TMS and BPSD) did not differ significantly on C-GAS scores \([F (2, 162) = 1.33, p = 0.27]\), however the means of C-GAS scores were in the anticipated direction. At Time 1, children with DSD + TMS \((M \pm SD = 44.8 \pm 7.1)\) had lower C-GAS scores than children with DSD \((M \pm SD = 46.5 \pm 7.0)\) but higher scores than children with BPSD \((M \pm SD = 43.1 \pm 8.8)\). The observed power of this test was 30%. The proportion of the effect and error variance that is attributable to the effect was negligible as evidenced by partial eta squared \((\eta_p^2 = 0.02)\).
Hypothesis two: Children with DSD + TMS at Time 1 will convert to BPSD at follow-up at a higher rate than children with DSD at Time 1. A Fisher’s Exact Test showed that children with DSD + TMS at Time 1 converted to BPSD at follow-up at a higher rate than children with DSD at Time 1 ($FET = 8.50, p = 0.01$) (see Table 3.2). The strength of the association between conversion rates and diagnosis status of the group was tested using Cramer’s $v$, which was found to be medium ($Cramer’s V = 0.55$). The odds of converting to BPSD were 6.5 times higher in children with DSD + TMS than children with DSD, however this ratio was not statistically significant ($CI_{95} = 0.69, 60.54$). (The calculation for odds ratio = probability of converting/probability of not converting = odds of DSD + TMS/odds of DSD = (DSD + TMS who converted to BPSD*DSD who did not convert to BPSD) / (DSD who converted to BPSD* DSD + TMS who did not convert to BPSD) = (7*12)/(1*13) = 6.46 times). The likelihood of BPSD in DSD + TMS group was 3.8 compared to the likelihood of BPSD in DSD group as evidenced by risk ratio; however, this ratio was not statistically significant ($CI_{95} = 0.58, 25.13$). (The calculation of risk ratio = proportion in DSD+ TMS group with BPSD condition present/proportion in DSD group with BPSD condition present = (7/13)/(1/12) = 0.48/0.125 = 3.84.)

<table>
<thead>
<tr>
<th>T1 Group$^a$</th>
<th>T4 Diagnosis DSD + TMS</th>
<th>T4 Diagnosis DSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSD + TMS</td>
<td>12 (48%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>DSD</td>
<td>1 (12.5%)</td>
<td>6 (75%)</td>
</tr>
</tbody>
</table>

$^a$p = 0.01, Fisher’s Exact Test

Note: T1 = Time 1; T4 = Time 4

Table 3.2 Conversion Rates of DSD + TMS and DSD to BPSD at Follow-up
Hypothesis three: Conversion rates will not differ for participants (DSD + TMS; n = 27) in the IMM (n = 12) and WLC group (n = 15) at Time 3. A Fisher’s Exact Test showed that the WLC group converted to BPSD at Time 3 at a higher rate than the IMM group ($FET = 6.61, p = 0.03$) (See Table 3.3). This analysis was conducted to examine the potential impact of treatment on conversion rates reported in hypothesis two. The strength of the association between conversion rates and treatment condition was tested using Cramer’s $v$, which was found to be medium (Cramer’s $V = 0.50$). The odds of converting to BPSD were 7.5 times higher in the WLC group than the IMM group, however this ratio was not statistically significant ($CI_{95} = 1.19, 47.05$). (The calculation for odds ratio = probability of converting/probability of not converting = odds of WLC/odds of IMM = (WLC who converted to BPSD*IMM who did not convert to BPSD) / (IMM who converted to BPSD* WLC who did not convert to BPSD) = (9*10)/(2*6) = 7.5 times.) The likelihood of BPSD in the WLC group was 3.6 compared to the likelihood of BPSD in IMM group as evidenced by risk ratio; however, this ratio was not statistically significant ($CI_{95} = 0.95, 13.62$). (The calculation of risk ratio = proportion in WLC group with BPSD condition present/proportion in IMM group with BPSD condition present = (9/6)/(2/10) = 0.60/0.17 = 3.6.)

<table>
<thead>
<tr>
<th>T1 DSD + TMS Group$^{a, b}$</th>
<th>T3 Diagnosis BPSD</th>
<th>T3 Diagnosis DSD + TMS</th>
<th>T3 Diagnosis DSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMM</td>
<td>2 (16%)</td>
<td>5 (42%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>WLC</td>
<td>9 (60%)</td>
<td>5 (33%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

Note. IMM = immediate treatment condition; WLC = 1-year waitlist control condition; T1 = Time 1; T3 = Time 3

$^{a} p = 0.03$, Fisher’s Exact Test; $^{b}$Values represent frequency (%)
Hypothesis four: The converted group (n = 12) will have greater impairment than the non-converted group (n = 13) on the following Time 1 variables (see Table 3.4):

a) Clinical presentation

The average impairment in clinical presentation was higher in the converted group \((M \pm SD = 3.9 \pm 1.6)\) than the non-converted group \((M \pm SD = 3.1 \pm 1.5)\) but this difference was not statistically significant \([t (23) = 1.35, p = 0.19]\). Using an alpha of 0.05, the observed power of this test was 30%. The practical significance was medium according to effect size \((d = 0.54)\).

b) Family environment

The average impairment in family environment was higher in the converted group \((M \pm SD = 3.0 \pm 1.7)\) than the non-converted group \((M \pm SD = 2.7 \pm 1.8)\) but the difference was not statistically significant \([t (22) = 0.42, p = 0.67]\). Using an alpha of 0.05, the observed power of this test was 7%. The practical significance was small according to effect size \((d = 0.17)\).

c) Family history

The average impairment in family history was higher in the converted group \((M \pm SD = 2.7 \pm 0.7)\) than the non-converted group \((M \pm SD = 2.1 \pm 1.4)\) but the difference was not statistically significant \([t (21) = 1.45, p = 0.17]\). Using an alpha of 0.05, the observed power of this test was 28%. The practical significance was medium according to effect size \((d = 0.60)\).
<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Converted</th>
<th>Non-converted</th>
<th>$p$</th>
<th>Power$^a$</th>
<th>$d^b$</th>
<th>Effect Size$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M (SD)$</td>
<td>$M (SD)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>3.9 (1.6)</td>
<td>3.1 (1.5)</td>
<td>0.19</td>
<td>30%</td>
<td>0.54</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>15.5 (6.9)</td>
<td>12.2 (7.8)</td>
<td>0.28</td>
<td>19%</td>
<td>0.44</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>38.0 (29.7)</td>
<td>42.4 (25.7)</td>
<td>0.70</td>
<td>7%</td>
<td>-0.16</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>43.8 (5.8)</td>
<td>49.5 (4.1)</td>
<td>0.009</td>
<td>80%</td>
<td>-1.14</td>
<td>L</td>
</tr>
<tr>
<td>Family Environment</td>
<td>3.0 (1.7)</td>
<td>2.7 (1.8)</td>
<td>0.67</td>
<td>7%</td>
<td>0.17</td>
<td>S</td>
</tr>
<tr>
<td>Life events</td>
<td>172.7 (160.0)</td>
<td>174.0 (121.3)</td>
<td>0.98</td>
<td>5%</td>
<td>-0.009</td>
<td>&gt;S</td>
</tr>
<tr>
<td>EEAC</td>
<td>18.3 (25.3)</td>
<td>28.7 (26.6)</td>
<td>0.32</td>
<td>12%</td>
<td>0.40</td>
<td>M</td>
</tr>
<tr>
<td>Family History</td>
<td>2.7 (0.7)</td>
<td>2.1 (1.4)</td>
<td>0.17</td>
<td>28%</td>
<td>0.60</td>
<td>M</td>
</tr>
<tr>
<td>Parental BPD</td>
<td>0.4 (0.7)</td>
<td>0.2 (0.4)</td>
<td>0.49</td>
<td>10%</td>
<td>0.29</td>
<td>S</td>
</tr>
<tr>
<td>2nd degree BPD</td>
<td>0.9 (1.7)</td>
<td>0.8 (1.4)</td>
<td>0.80</td>
<td>6%</td>
<td>0.11</td>
<td>S</td>
</tr>
<tr>
<td>Loaded history$^e$</td>
<td>6.4 (3.5)</td>
<td>5.0 (2.7)</td>
<td>0.29</td>
<td>5%</td>
<td>0.45</td>
<td>M</td>
</tr>
<tr>
<td>Parental MSI</td>
<td>11.6 (9.8)</td>
<td>6.2 (6.1)</td>
<td>0.11</td>
<td>6%</td>
<td>0.67</td>
<td>M</td>
</tr>
</tbody>
</table>

*Note:* MRS = prodromal manic symptoms; EEAC = critical and hostile family environment; MSI = Mood Severity Index.

$^a$ Observed power calculated using an alpha of 0.05; $^b$ Cohen’s effect size; $^c$ S = small, M = medium, L = large; $^d$ prodromal duration; $^e$ loaded family history major affective disorder scale.

Table 3.4: Differences Between the Converted and the Non-converted Groups on Clinical Presentation, Family Environment, Family History and Their Components

*Secondary Analyses: The converted group (n = 12) will differ from the non-converted group (n = 13) on the following Time 1 variables (see Table 3.4):*

1. **Clinical presentation:**

   a) **Greater severity of prodromal manic symptoms**

   The average severity of prodromal manic symptoms was higher in the converted group ($M \pm SD = 15.5 \pm 6.9$) than the non-converted group ($M \pm SD = 12.2 \pm 7.8$) but
the difference was not statistically significant \( t(23) = 1.11, p = 0.28 \). Using an alpha of 0.05, the observed power of this test was 19%. The practical significance of the difference was medium according to effect size \( d = 0.44 \).

b) Longer duration of prodromes

A two-sample t-test revealed that the converted group did not differ significantly compared to the non-converted group on duration of prodromes \( t(23) = -0.40, p = 0.70 \). Interestingly, findings were in the reverse direction; the mean duration of prodromes was longer for the non-converted group \( (M \pm SD = 42.4 \pm 25.7) \) than the converted group \( (M \pm SD = 38.0 \pm 29.7) \). Using an alpha of 0.05, the observed power of this test was 7%. The practical significance of the difference was small according to effect size \( d = -0.16 \).

c) Lower C-GAS scores

A two-sample t-test revealed that the average Time 1 C-GAS score was significantly lower in the converted group \( (M \pm SD = 43.8 \pm 5.8) \) than the non-converted group \( (M \pm SD = 49.5 \pm 4.1) \) \( t(23) = -2.84, p = 0.009 \). Using an alpha of 0.05, the observed power of this test was 80%. The practical significance of the difference was large according to effect size \( d = -1.14 \)

2. Family environment:

a) Greater number of life events

A two-sample t-test showed that the average number of life events did not differ significantly between the converted group and the non-converted group \( t(22) = -0.02, p = 0.98 \). The means were in the reverse direction from the hypothesized results. The converted group reported a lower number of life events
than the non-converted group \((M \pm SD = 174.0 \pm 121.3)\).  
Using an alpha of 0.05, the observed power of this test was 5%.  The practical significance of the difference was negligible according to effect size \((d = -0.009)\).

\(b)\)  More critical and hostile family environment

The mean level of critical and hostile family environment was lower (of note, lower EEAC scores indicate higher critical and hostile family environment) for the converted group \((M \pm SD = 18.3 \pm 25.3)\) than the non-converted group \((M \pm SD = 28.7 \pm 26.6)\) but this difference was not statistically significant \([t(23) = -1.00, p = 0.32]\).  Using an alpha of 0.05, the observed power of this test was 12%.  The practical significance of the difference was medium according to effect size \((d = 0.40)\).

3.  Family history:

\(a)\)  Higher scores on parental BPD scale

The mean score on the parental BPD scale was higher in the converted group \((M \pm SD = 0.4 \pm 0.7)\) than the non-converted group \((M \pm SD = 0.2 \pm 0.4)\) but the difference was not statically significant \([t(21) = 0.71, p = 0.49]\).  Using an alpha of 0.05, the observed power of this test was 10%.  The practical significance of the difference was small according to effect size \((d = 0.29)\).

\(b)\)  Higher scores on second degree relatives’ BPD scale

The mean score on the second degree relatives’ BPD scale was higher in the converted group \((M \pm SD = 0.9 \pm 1.7)\) than the non-converted group \((M \pm SD = 0.8 \pm 1.4)\) but the difference was not statistically significant \([t(20) = 0.25,\)
Using an alpha of 0.05, the observed power of this test was 6%. The practical significance of the difference was small according to effect size ($d = 0.11$).

c) **Higher scores on loaded family history major affective disorder scale**

The mean scores on loaded family history major affective disorder scale was higher in the converted group ($M \pm SD = 6.4 \pm 3.5$) than the non-converted group ($M \pm SD = 5.0 \pm 2.7$) but the difference was not statistically significant [$t (21) = 1.09, p = 0.29$]. Using an alpha of 0.05, the observed power of this test was 5%. The practical significance of the difference was medium according to effect size ($d = 0.45$).

d) **Higher mood severity in the parent as measured by the MSI.**

The average mood severity index in the parent was higher in the converted group ($M \pm SD = 11.6 \pm 9.8$) than the non-converted group ($M \pm SD = 6.2 \pm 6.1$) but the difference was not statistically significant [$t (23) = 1.69, p = 0.11$]. Using an alpha of 0.05, the observed power of this test was 6%. The practical significance of the difference was medium according to effect size ($d = 0.67$).

**IMM and WLC treatment condition influences.** As the WLC group converted at a higher rate than the IMM group, frequencies for change in service utilization were calculated to assess the possible influence of treatment condition on conversion rates (see Table 3.5).
<table>
<thead>
<tr>
<th>Service Utilization&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IMM&lt;sup&gt;b&lt;/sup&gt; n = 12</th>
<th></th>
<th></th>
<th>WLC&lt;sup&gt;b&lt;/sup&gt; n = 14</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Converters</td>
<td>Non-converters</td>
<td>Converters</td>
<td>Non-converters</td>
<td>Converters</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (50%)</td>
<td>8 (80%)</td>
<td>3 (37.5%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>1 (50%)</td>
<td>2 (20%)</td>
<td>3 (37.5%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>School</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16.7%</td>
<td>7 (70%)</td>
<td>4 (50%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
<td>2 (25%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>0 (0%)</td>
<td>4 (40%)</td>
<td>4 (50%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2 (100%)</td>
<td>1 (10%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (50%)</td>
<td>7 (70%)</td>
<td>3 (37.5%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>0.33 (17%)</td>
<td>2 (20%)</td>
<td>3 (37.5%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.67 (33%)</td>
<td>1 (10%)</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Change direction from Time 1 to Time 3;  <sup>b</sup>Values represent frequency (%)

Table 3.5. Frequency of Change in Service Utilization for IMM and WLC Groups

*Converted group manic characteristics (n = 12).* Five children converted to BPSD at Time 2, five at Time 3 and two at Time 6. Of the 12 who converted, three children converted to BP-I, five to BP-II, three to BP-NOS and one to mood disorder due to general medical condition and/or substance induced. The frequency of manic symptoms endorsed on the MRS was calculated to understand the manic symptom characteristics of DSD + TMS at Time 1 and at the time point they converted to BPSD (see Table 3.6).
### Table 3.6. Frequency of Manic Symptoms at Time 1 and Converted Time Point for the Converted Group

<table>
<thead>
<tr>
<th>Manic Symptoms</th>
<th>Time 1</th>
<th>Converted Time-point&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Change Direction&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated mood</td>
<td>8%</td>
<td>58%</td>
<td>↑</td>
</tr>
<tr>
<td>Irritability</td>
<td>83%</td>
<td>75%</td>
<td>↓</td>
</tr>
<tr>
<td>Content</td>
<td>25%</td>
<td>42%</td>
<td>↑</td>
</tr>
<tr>
<td>Sleep</td>
<td>8%</td>
<td>25%</td>
<td>↑</td>
</tr>
<tr>
<td>Language-thought disorder</td>
<td>33%</td>
<td>25%</td>
<td>↓</td>
</tr>
<tr>
<td>Speech (rate and amount)</td>
<td>50%</td>
<td>75%</td>
<td>↑</td>
</tr>
<tr>
<td>Increased motor activity/energy</td>
<td>0%</td>
<td>67%</td>
<td>↑</td>
</tr>
<tr>
<td>Sexual interest</td>
<td>8%</td>
<td>25%</td>
<td>↑</td>
</tr>
<tr>
<td>Disruptive-aggressive behavior</td>
<td>75%</td>
<td>58%</td>
<td>↓</td>
</tr>
<tr>
<td>Appearance</td>
<td>17%</td>
<td>33%</td>
<td>↑</td>
</tr>
<tr>
<td>Insight</td>
<td>25%</td>
<td>33%</td>
<td>↑</td>
</tr>
</tbody>
</table>

<sup>a</sup> five converted at Time 2, five at Time 3 & two at Time 4; <sup>b</sup> from Time 1 to converted time-point

**Power analyses.** Power analyses using Dean and Voss’ methodology (1999) was calculated to determine the sample sizes, assuming power of 0.8 and alpha of 0.05, needed to test hypothesis one in future studies. For both hypotheses one and four, 55 participants per group would be needed.

**ITT analyses.** To further understand Hypothesis two, three, four and secondary analyses, intent-to-treat analyses were conducted to account for study drop-outs.

Seventeen drop-outs from DSD and TMS and DSD group had their last observation carried forward (LOCF) to impute eighteen month missing data, which resulted in 37 participants for the DSD + TMS group and 13 for the DSD group. ITT analysis for hypothesis two confirmed the earlier findings that children with DSD + TMS at Time 1
converted to BPSD at follow-up at a higher rate than children with DSD at Time 1
\((FET = 20.36, p = 0.000)\). The strength of the association between conversion rates and
diagnosis status of the group was tested using Cramer’s \(v\), which was found to be
medium (Cramer’s \(V = 0.67\)). The odds of converting to BPSD was 4.2 times higher in
children with DSD + TMS than children with DSD; however, this ratio was not
statistically significant \((CI_{95} = 0.60, 29.33)\). The likelihood of BPSD in the DSD + TMS
group was 5.8 compared to the likelihood of BPSD in the DSD group as evidenced by
risk ratio; however, this ratio was not statistically significant \((CI_{95} = 0.67, 49.60)\). ITT
analysis for hypothesis three indicated that the difference in conversion rates for
participants (DSD + TMS) in the IMM \((n = 17)\) and in the WLC \((n = 20)\) group at Time 3
were marginally significant \((FET = 5.44, p = 0.07)\). The strength of the association
between conversion rates and treatment group was tested using Cramer’s \(v\), which was
found to be small (Cramer’s \(V = 0.39\)). The odds of converting from DSD + TMS to
BPSD was 6.1 times higher in children in the WLC group than children in the IMM
group; however, this ratio was not statistically significant \((CI_{95} = 0.95, 15.34)\). The
likelihood of BPSD in the WLC group was 3.8 compared to the likelihood of BPSD in
the IMM group as evidenced by risk ratio; however, this ratio was not statistically
significant \((CI_{95} = 1.10, 34.22)\). ITT analysis for hypothesis four confirmed earlier
findings that the converted group did not significantly differ from the non-converted
group on composite variables of clinical presentation, \([t (35) = -0.94, p = 0.35]\); family
environment, \([t (31) = -0.53, p = 0.60]\); and family history, \([t (32) = 0.77, p = 0.45]\). The
practical significance was small according to effect size \((d = -.33, -.20, .25, \text{respectively})\).
Finally, ITT analyses for supplementary hypotheses showed that the converted group did
not significantly differ than the non-converted group on level of severity of prodromal manic symptoms, \([t (35) = -0.34, p = 0.74]\); duration of prodromes, \([t (35) = -0.78, p = 0.44]\); C-GAS scores, \([t (35) = 0.31, p = 0.76]\); number of life events, \([t (31) = -0.26, p = 0.80]\); level of hostile and critical family environment, \([t (35) = -0.05, p = 0.96]\); parental BPD scale, \([t (32) = 0.64, p = 0.53]\); second degree relatives’ BPD scale, \([t (31) = 0.98, p = 0.34]\); loaded family history major affective disorder scale, \([t (32) = 1.56, p = 0.13]\); and MSI in parents, \([t (35) = 0.69, p = 0.50]\). The practical significance was small according to effect size for prodromal manic symptoms \((d = -0.12)\), duration of prodromes \((d = -0.27)\), C-GAS scores \((d = -0.11)\), number of life events \((d = -0.09)\), level of hostile and critical family environment \((d = -0.02)\), parental BPD scale \((d = 0.22)\), second degree relatives’ BPD scale \((d = 0.33)\) and MSI in parents \((d = 0.23)\). The practical significance was medium according to effect size for loaded family history major affective disorder scale \((d = 0.56)\). The significant difference observed on C-GAS scores earlier was not observed in ITT analyses.

**Additional analyses.** Seven out of nine comparisons in the supplementary hypotheses were in the predicted direction. Due to small sample sizes (converted group, \(n = 12\); non-converted group, \(n = 13\)), it is probable the data did not meet the assumption of 2 independent sample t-test, so a nonparametric procedure was utilized. A Mann-Whitney \(U\) test was conducted to see whether the converted group and the non-converted group were from different sample distributions. The converted group and the non-converted group were from similar sample distributions for: severity of prodromal manic symptoms, \((U = 56.0, p = 0.23)\); duration of prodromes, \((U = 69.5, p = 0.64)\); life events, \((U = 68.0, p = 0.84)\); critical and hostile family environment,
(U = 56.5, p = 0.24); parental BPD scale, (U = 58.5, p = 0.57); second degree relatives’
BPD scale, (U = 60.0, p = 0.97); loaded family history major affective disorder scale,
(U = 49.5, p = 0.31). A significant difference was noted in the sample distributions of
C-GAS scores for the converted group and the non-converted group (U = 34.5, p = 0.02).
Also, a marginally significant difference was found comparing the sample distributions of
mood severity index in parents for the converted group and the non-converted group
(U = 44.0, p = 0.07).
Chapter 4: Discussion

No studies have assessed the rates of conversion to BPSD in children with DSD + TMS. TMS are defined as manic-like symptoms of insufficient duration or number to warrant a diagnosis of BPSD. Studying rates of conversion from DSD to BPSD allows for the assessment of risk factors that can predict bipolarity in this sample. There were several goals in the current study. The first goal was to compare C-GAS scores for the children with DSD + TMS to the children with DSD and to the children with BPSD at Time 1. The second goal was to assess how many children with DSD + TMS converted to BPSD during follow-up in comparison to children with DSD. Third, I sought to rule out treatment effects that can explain the conversion rates for DSD + TMS in the IMM and WLC group. Fourth, I assessed which variables (clinical presentation, family environment and/or family history) might predict conversion to BPSD at follow-up in DSD + TMS population. Moreover, I sought to assess which components (prodromal mood severity, duration of prodromes, C-GAS scores, life events, critical and hostile family environment, parental BPD scale, second degree relatives’ BPD scale, loaded family history major affective disorder scale and mood severity index in parents) of the composite variables (clinical presentation, family environment and family history) might predict conversion to BPSD at follow-up in DSD + TMS population. The final goal was to determine sample sizes needed to conduct
more refined tests of the relationship between diagnostic status of participants and C-GAS score and the relationship between risk factors and conversion to BPSD. In the following discussion, I interpret results of hypotheses testing, discuss clinical implications, clinical descriptions of converters, limitations and goals for future research.

Comparison of Global Functioning Impairment in BPSD, DSD + TMS and DSD

In this study, there were no significant differences between BPSD, DSD + TMS and DSD groups on impairment in global functioning (C-GAS scores); however, the means were in the anticipated direction, with children with DSD + TMS having lower levels of C-GAS scores than children with DSD but higher scores than children with BPSD. C-GAS scores less than or equal to 60 are considered impaired in their functioning to warrant a diagnosis (Geller, Bolhofner, Craney, Williams, DelBello & Gundersen, 2000). The average scores for all three groups fell in the C-GAS index range of 50-41. Shaffer and colleagues (1983) describe this range as a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area.

This finding has two possible explanations. First, it is possible that all three groups (DSD, DSD + TMS and BPSD) are moderately to severally impaired in their functioning at home, school, and/or with peers and that diagnostic status at Time 1 may not dictate the level of global impairment. Second, power analyses indicated that a larger sample size (55 participants per group) may be needed to detect statistical significance. DSD + TMS and BPSD had less than 55 participants in the group. As the means were in the predicted direction and the observed power of this test was 30%, it is possible that with larger samples and greater variability in each group a significant difference among
groups would be found on C-GAS scores. However, as the effect size was negligible, C-GAS score may not be a useful factor in assessing impairment level based on diagnostic status (i.e., BPSD, DSD + TMS, and DSD) of the participants.

**Conversion Rates from DSD + TMS and DSD to BPSD**

The clinical importance of subsyndromal transient manic symptoms in children have not been examined longitudinally to determine whether these subthreshold transient manifestations later progress to a recognized bipolar spectrum disorder. In the present study, over an 18-month follow-up period, children with DSD + TMS at Time 1 converted at a significantly higher rate than children with DSD at Time 1. The rate of conversion from DSD + TMS to subsequent BPSD was 48% whereas the rate of conversion from DSD to subsequent BPSD was 12.5%. The strength of association between conversion rates and diagnostic status of the group was medium. The odds of converting to BPSD were 6.5 times higher in children with DSD + TMS than children with DSD; however, this ratio was not statistically significant. The likelihood of BPSD in DSD + TMS group was 3.8 compared to the likelihood of BPSD in DSD group as evidenced by risk ratio; however, this ratio was not statistically significant. This may be because of the small sample size in each group. As conversion rates were significant, perhaps with larger samples, the odds ratio of converting from DSD + TMS to BPSD and the relative risk would be significant. The rate of conversion for children with DSD + TMS to subsequent BPSD was 60% in the WLC group compared to 16% in the IMM group. The odds of converting to BPSD were 7.5 times higher in WLC group than IMM group, however this ratio was not statistically significant. The likelihood of BPSD in WLC group was 3.6 compared to the likelihood of BPSD in the IMM group as
evidenced by risk ratio; however, this ratio was not statistically significant. This finding was in the unanticipated direction.

MFPG treatment goal includes better service utilization due to teaching children and parents to be better consumers of mental health care. Service utilization was assessed in four areas – medication, school, therapy and overall. The change score was calculated by deducting Time 1 service utilization score from Time 3 service utilization score for each of these four areas. While the sample size was small, participating in the MFPG treatment appeared to be protective as families may have become more judicious in their usage of medication, school services, therapy and overall service. However, it is possible that the participants with negative change scores may have been doing worse from the beginning, therefore, making it harder for them to get better. Overall, contrary to the hypothesis, this finding suggests that psychoeducation for parents and children with mood disorders can be beneficial.

Even though no studies have assessed the rates of conversion to BPSD in children with DSD + TMS, several studies have assessed conversion rates from unipolar disorder to BPD in adult and youth populations. Retrospective and prospective studies indicates that 50% or more adults with BPD report their age of onset prior to 19 years and a sizable minority (14-33%) report their age of onset prior to 14 or 15 years (Chengappa et al., 2003; Hirschfeld, Lewis and Lana, 2003; Leverich, 2007). In these studies over half experienced a depressive episode first, highlighting the importance of tracking manic symptoms in individuals with depression. Rates of conversion from unipolar disorder to subsequent BPD in adult populations ranged from 12.5% in an outpatient sample followed for 11 years to 45-50% in an inpatient sample followed for 15 to 23 years.
(Akiskal et al., 1995; Goldberg, Harrow & Whiteside, 2001; Angst, Sellaro, Stassen & Gamma, 2005). Prospective studies indicate that the rate of conversion from MDD to BP-I and BP-II in prepubertal children and adolescent was in the range of 20% to 48.6%, depending on the length of follow-up (Strober & Carlson, 1982; Geller, Fox & Clark, 1994; Geller, Zimerman Williams, Bolhofner & Craney, 2001). The conversion rate to BPSD in the pure DSD group (12.5%) in the present study is less than past figures reported in youth (33% to 48% outpatient children and adolescent sample followed within 2-10 years; Geller, Fox & Clark, 1994; Geller, Zimmerman Williams, Bolhofner & Craney, 2001). It is possible this is due to the relatively brief follow-up duration for the current study (18 months). Also, other studies have not separated out “pure” DSD participants from those with DSD and transient manic symptoms. If the two samples (DSD and DSD+TMS) in this study were combined, there would have been a conversion rate of 39.4%, which is more consistent with that previously reported in the literature.

Transient manic symptoms (TMS) are, by definition, insufficient to warrant a bipolar diagnosis. However, they should serve as a warning signal to monitor the potential for conversion. This is particularly important, as pharmacologic treatments for children with depression and/or with a co-morbid condition of ADHD can destabilize children with BPD (Reichart & Nolen, 2004). Reichart and Nolen (2004) hypothesize that using antidepressants and stimulants with children who are genetically at risk of developing BPSD may trigger a manic episode. In a retrospective study by DelBello and colleagues (2001), age of onset was compared between adolescents with BPD either with or without a history of stimulant use. Earlier age of onset was observed in adolescents with BPD who have a prior history of stimulant intake ($M \pm SD$ age at onset of
BPD = 10.7 ± 3.9) compared to adolescents with BPD who have no prior history of stimulant intake ($M \pm SD$ age at onset of BPD = 13.9 ± 3.7). Also, the co-morbidity of behavior disorder was high in adolescents with BPD with a history of stimulants (81% ADHD; 43% conduct disorder; 48% oppositional defiant disorder) compared to adolescents with BPD without a history of stimulants (38% ADHD; 15% conduct disorder; 38% oppositional defiant disorder). Children with DSD and/or ADHD may be initially treated with antidepressants and/or stimulants prior to the onset of BPD, which may cause earlier onset of BPD. Therefore, early recognition is a critical component to quality care. Studying rates of conversion from DSD + TMS to BPSD allows for the assessment of risk factors for conversion to bipolarity in this sample.

*Risk Factors Associated with Conversion from DSD + TMS to BPSD*

To assess risk factors associated with conversion to BPSD in DSD + TMS group I calculated three composite variables. They were clinical presentation, family history and family environment. I also looked at the individual components of these composite variables as possible risk factors to explain conversion rates. The converted group (i.e., children with DSD + TMS who converted to BPSD at follow-up) was compared with the non-converted group (i.e., children with DSD + TMS who did not convert to BPSD) on risk factors.

*Clinical presentation.* The converted group and the non-converted group did not differ significantly on average ratings of the clinical presentation composite variable; however the means were in the predicted direction. The observed power of this test was
30% and the practical significance was medium according to effect size. I hypothesize that using larger samples and with greater variability, significant differences would be found in clinical presentation.

The components of the clinical presentation composite variable were severity of prodromal manic symptoms, duration of prodromes and C-GAS scores. As hypothesized, the converted group ($M \pm SD = 43.8 \pm 5.8$) had significantly lower C-GAS scores than the non-converted group ($M \pm SD = 49.5 \pm 4.1$) indicating that converted group was more impaired in their global functioning than the non-converted group. Observed power of this test was adequate to detect the difference in C-GAS scores and the effect size of this finding was large. C-GAS is a measure for assessing impairment in functioning at school, home and with peers and can be used by clinicians as a risk factor when assessing children with DSD + TMS for a possible future conversion to BPSD.

The converted group did not significantly differ on severity of prodromal manic symptoms and duration of prodromes; however, the means were in the anticipated direction for prodromal manic symptoms, but in the opposite direction for duration of prodromes. The converted group reported greater severity of prodromal manic symptoms than the non-converted group. The observed power of the test for prodromal manic symptoms was 19% and the effect size was medium. I hypothesize that with larger samples and greater variability, significant differences would be found between both groups on prodromal manic symptoms.

The converted group had a shorter duration of prodromes than the non-converted group. The observed power of this test was 7% and the effect size was small. Duration of prodromes in the present study was calculated by subtracting age of onset for prodromal
symptoms from age of onset of the first mood episode. Past research on prodromal symptoms in adult populations with BPD indicates that the mean duration of manic prodromes is longer than depressive prodromes (Jackson, Cavanagh & Scott, 2003). In the future, it may be useful to assess duration of prodromes for manic symptoms as the method in the current study did not distinguish between manic or depressive symptoms.

*Family environment.* The converted group and the non-converted group did not differ significantly on average ratings of the family environment composite variable, even though their means were in the hypothesized direction. The observed power of this test was very low (7%) and the effect size was small.

Components of the family environment composite variable were life events and a critical and hostile family environment. The converted group did not significantly differ on life events and critical and hostile family environment from the non-converted group. However, the means were in the anticipated direction for the critical and hostile family environment, but in the unanticipated direction for life events.

As hypothesized, the converted group reported higher levels of criticism and hostility in the family environment than the non-converted group. The observed power for this test was 12% and the effect size was medium. I hypothesize that with larger sample size and greater variability statistically significant difference may be found in critical and hostile family environment.

A more critical and hostile family environment (EE) is associated with higher relapse rates (Miklowitz et al., 1988) and lower rates of recovery (Asarnow et al. 1993). EE is found to be a valid predictor of outcome in patients with major depressive disorder and BPD (Hooley & Hiller, 2001). The diathesis-stress model (Meehl, 1962) suggests
that both biological and environmental factors may influence the onset of a disorder. For example, in an individual with high genetic vulnerability, little stress can influence onset of the disorder whereas in an individual with low genetic vulnerability, higher levels of stress may be necessary. A diathesis-stress model can explain onset as well as relapse of psychological disorders (Hooley & Hiller, 2001).

Contrary to the hypothesis, the converted group reported a (negligibly) lesser number of life events than the non-converted group. Past research indicates that more stressful events are seen prior to manic episodes compared to control (Goodwin and Jamison 2007, p. 138). For example, stressful life events may cause a loss of sleep, which in turn can trigger an onset of mania. We had hypothesized that stressful life events may trigger an episode of mania in patients diagnosed with unipolar depression who have a vulnerability to develop BPD. However, the effect size of this test was negligible suggesting that life events may not a useful risk factor to explain conversion rates.

*Family history.* Family, twin and adoption studies demonstrate the influence of genetic transmission in BPD and MDD (Goodwin & Jamison, pp. 414-422).

In the present study, the converted group and the non-converted group did not differ significantly on family history composite average ratings, even though their means were in the hypothesized direction. The observed power of this test was low (28%) and the effect size was medium. I hypothesize that with a larger sample size and greater variability statistically significant differences may be found.

The components of the family history composite variable were the parental BPD scale, the second degree relatives’ BPD scale, the loaded family history major affective
disorder scale, and mood severity index in parents. The converted group did not significantly differ on the parental BPD scale, the second degree relatives’ BPD scale, the loaded family history major affective disorder scale, and a mood severity index in parents from the non-converted group; however, the means were in the anticipated direction for all four variables. A marginally significant difference was found comparing the sample distributions of mood severity index in parents for the converted group and the non-converted group. As hypothesized the converted group had higher scores on the parental BPD scale, higher scores on the second degree relatives’ BPD scale, higher scores on the loaded family history major affective disorder (BPD, major depression, and schizoaffective disorder) scale, and higher levels of mood severity in parents than the non-converted group.

There are several possible explanations for these findings: (1) the sample size may have been too small to detect statistical significance. However, the observed powers of these four tests ranged from 5% to 10% and the practical significance ranged from small to medium. I hypothesize that with larger sample size and greater variability, statistically significant difference may be found in the parental BPD scale, the second degree relatives’ BPD scale, the loaded family history major affective disorder scale and mood severity index in parents; (2) primary informants had to recall the family history of affective disorders (BP, MDD and SA) for themselves, the other biological parent and second degree relatives. As discussed in the method section, FH-RDC has good diagnostic reliability for high-threshold diagnoses (depression, alcoholism, drug abuse and antisocial personality), but low diagnostic reliability for other psychiatric diagnosis (Zimmerman, Coryell, Pfohl & Stangl, 1988). It is possible that the information collected
on BPD and schizoaffective disorder may be influenced by these problems with the instrument. Also, the family history method can underestimate the prevalence rates due to underreporting of relatives diagnoses in relatives (e.g., forgetting or omitting family members with a psychiatric diagnosis, not remembering “unpleasant and distant” relatives, anxiety about psychiatric illness may cause forgetting) (Baker, Berry & Adler, 1987), underreporting of one’s own diagnoses, and lack of accurate information on biological parents and second degree relatives’ of adopted and foster children. Using a direct interview method may be more accurate (Vandeleur et al. 2008); however, it can be expensive and time consuming. A less expensive method may be to construct a family tree in addition to FH-RDC, the strategy employed in this study, which may ensure less forgetting by informants (Baker, Berry & Adler, 1987). Gathering information about a family history can help clinicians in forming an accurate diagnosis (Baker, Berry & Adler, 1987). Also, it is important for clinicians to be aware of the family mental health history and mood severity in parents, for, in addition to genetic influence, it can also impact the family atmosphere, thereby affecting the course and prognosis of the disorder for children (Chang, Steiner & Ketter, 2000).

*Clinical Descriptions of Converters*

At Time 1, children with DSD + TMS showed varying prodromal manic symptoms, most commonly irritability (83%) and disruptive aggressive behavior (75%), neither of which are exclusive to BPD. Other manic symptoms were present to a lesser extent including speech (50%), language thought disorder (33%), insight (25%), content (25%), appearance (17%), sexual interest (8%), elevated mood (8%), and sleep (8%). At conversion, these children still demonstrated higher rates of irritability (75%) and...
disruptive aggressive behavior (58%), but also commonly had speech (75%), increased motor activity (67%), elevated mood (58%) and content (42%). A sizable minority demonstrated appearance (33%), insight (33%), sexual interest (25%), sleep (25%), and language thought disorder (25%). Of note, when children were diagnosed with a BPSD, symptoms of irritability and disruptive and aggressive behavior actually declined in comparison to their frequency at Time 1. Except for increased motor activity, all other symptoms were observed at both Time 1 and the time of conversion, albeit with different frequencies.

Transient manic symptoms such as irritability and disruptive aggressive behavior can serve as warning signal when assessing DSD + TMS population. These symptoms may act as precursors to impending conversion. Past research indicates that 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 (Chang, Steiner & Ketter, 2000). Past retrospective research with adults self-identified as having BPD indicates that a majority of respondents (70%) had experienced at least one impairing manic symptom for some time prior to their BPD diagnosis (Hirschfeld, Lewis & Vornik, 2003). These symptoms included erratic sleeping, elevated mood, racing thoughts, increased speech, impulsiveness, increased physical and/or mental activity, and poor judgment. Of note, two-thirds (67%) of respondents experienced excessive irritability and aggressive behavior, while 57% experienced reckless behavior. Further, misdiagnosis was common; over two-thirds (69%) of the sample reported having been misdiagnosed, most frequently with unipolar depression.
When reviewing prodromal manic symptoms in the present study, a higher frequency of irritability and disruptive, aggressive behavior was observed in the converted group than on the non-converted group. Chang and colleagues (2000) recommend treating prodromal manic symptoms to prevent them from developing manic episodes. Also, treating these children with antidepressants and/or stimulants may trigger or worsen childhood mania (Geller et al., 1992).

Conclusions and Clinical Implications

The level of impairment in global functioning did not differ significantly between DSD, DSD + TMS, and BPSD at Time 1. Power analyses indicated this may be because the sample size may have been too small to detect statistical significance. The rates of conversion to BPSD at follow-up were significantly higher in children with DSD + TMS than children with DSD, highlighting the importance of assessing transient manic symptoms in DSD population. The odds of converting to BPSD were 6.5 times higher in children with DSD + TMS than children with DSD. There are several clinical implications of this finding. First, these transient manic symptoms should serve as a warning signal for clinicians and doctors to monitor the potential for conversion. Second, as pharmacologic treatments for children with depression can destabilize children with BPSD, these transient manic symptoms can be used to guide pharmacologic treatment. Finally, awareness should be raised of both the importance of monitoring transient manic symptoms and the potential for conversion to BPSD amongst parents and children.

The rates of conversion from DSD + TMS to BPSD at Time 3 were significantly higher for the WLC group. This suggests being in psychoeducational treatment like
MFPG may be protective. By teaching parents to become better consumers of care, parents are able to assemble more effective treatment plans for their children.

The converted group did not significantly differ from the non-converted group on clinical presentation, family environment and family history. Further these two groups did not differ significantly on severity of manic symptoms, duration of prodromes, a critical and hostile family environment, life events, the parental BPD scale, the second degree relatives’ BPD scale, the loaded family history major affective disorder scale, and a mood severity index in parents. However, the two groups differed significantly on C-GAS scores. Also, marginally significant differences were observed on sample distribution of mood severity index in parents. C-GAS score can be useful for clinicians when assessing a DSD + TMS population. Also, parental mood dysregulation can influence the family environment, which can impact the course and prognosis of BPSD in children with DSD + TMS. When reviewing prodromal manic symptoms in the converted group in the present study, a higher frequency of irritability and disruptive, aggressive behavior was observed at Time 1 compared to the converted time-point. Except for increased motor activity, all other symptoms were observed at both Time 1 and the time of conversion, albeit with different frequencies.

Clinicians should inquire about transient prodromal manic symptoms in DSD populations. These transient manic symptoms should be monitored by mental health providers and parents. Treating prodromal manic symptoms to prevent them from developing manic episodes may be beneficial (Chang, Steiner & Ketter, 2000). Also treating these children with antidepressants and/or stimulants may trigger or worsen
childhood mania (Geller et al., 1992). Parents may benefit from education about these symptoms and possible treatment options.

**Limitations and Directions for Future Research**

There were several limitations in the present study. First, the sample size in DSD + TMS and DSD group was small \( n = 50 \) at Time 1 and even smaller at follow-up \( n = 33 \). Also, sample sizes of the converted group \( n = 12 \) and the non-converted group \( n = 13 \) were small at follow-up. Larger sample sizes would be beneficial. Second, the restricted racial demographics of the present study (i.e., predominantly White) limits the generalizability of these findings to other populations. Studies assessing risk factors associated with conversion rates in different races would be beneficial. Third, as these were exploratory hypotheses, corrections were not made for multiple comparisons. Fourth, the length of the study may be inadequate to assess risk factors associated with conversion. Future studies should examine at risk factors associated with conversion over a longer follow-up period. Also, future research should focus on assessing the influence of pharmacotherapy on transient manic symptoms and subsequent conversion to BPSD.
References


