Published in final edited form as:

J Abnorm Child Psychol. 2012 April ; 40(3): 339–351. doi:10.1007/s10802-011-9568-5.

Anxiety in Children with Mood Disorders: A Treatment Help or Hindrance?

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Abstract

This study examined the role of comorbid anxiety in treatment outcome for children with mood disorders ($N=165$; age 8–11) participating in Multi-Family Psychoeducational Psychotherapy (MF-PEP). Assessments occurred at baseline, 6, 12, and 18 months for two randomly assigned groups: immediate treatment and 1-year wait-list. Most children (69%) had comorbid anxiety disorders. Baseline comorbid anxiety, as reported on the Children's Interview for Psychiatric Syndromes (ChIPS), was associated with higher Children's Depression Rating Scale- Revised (CDRS-R) scores but not Young Mania Rating Scale (YMRS) scores. Higher levels of anxiety symptoms were associated with lower Children's Global Assessment Scale (C-GAS) scores. Participation in MF-PEP did not significantly reduce anxiety symptoms ($p=0.62$). However, presence of comorbid anxiety did not impede reduction in depressive (CDRS-R, $p=0.74$) or manic (YMRS scores, $p=0.94$) symptoms following MF-PEP. More baseline anxiety symptoms were associated with greater improvement in C-GAS scores post-treatment ($p=0.02$). Implications are discussed.

Keywords

Comorbidity; Mood disorders; Anxiety; Children

Mood disorders in childhood are associated with significant morbidity, mortality, distress and impairment (Stark et al. 1996; Weckerly 2002; Weissman et al. 1999; Wozniak et al. 2004). Further complicating research and treatment of childhood mood disorders are comorbid conditions, which are the rule, not the exception (Wozniak et al. 2004; Yorbik et al. 2004). Comorbid anxiety disorders are particularly common in children with mood disorders (Harpold et al. 2005; Lewinsohn et al. 1997). Pediatric anxiety disorders are associated with significant impairment (Greco and Morris 2005; Van Amerigen et al. 2003;

Verduin and Kendall 2008) and poor prognosis (Aschenbrand et al. 2003; Woodward and Fergusson 2001), suggesting comorbid anxiety may contribute to increased difficulty among children with mood disorders. Despite this, few studies have examined the effect of anxiety disorders on treatment outcome in children with mood disorders (Seligman and Ollendick 1998).

This paper: reviews current research regarding comorbidity of anxiety disorders with depressive spectrum disorders (DSD-major depressive disorder [MDD] and/or dysthymic disorder [DD]) and bipolar spectrum disorders (BPSD-bipolar disorder type I [BP-I], BP type II [BP-II], BP Not Otherwise Specified [BP-NOS], or cyclothymic disorder [CYC]), particularly the impact of anxiety disorders on treatment response; briefly describes a new psychosocial treatment modality for children with mood disorders, Multi-Family Psychoeducational Psychotherapy (MF-PEP; Fristad et al. 2011); and examines the impact of anxiety symptoms on MF-PEP treatment outcome for children with mood disorders, as well as the impact of MF-PEP on anxiety symptoms.

Comorbidity of Anxiety with DSD

Anxiety disorders are the most common co-occurring psychiatric disorders in children with DSD, with estimates ranging from 20% to 75% (Avenevoli et al. 2001; Masi et al. 2001a; Yorbik et al. 2004). Additionally, anxiety often precedes depression. In one study, two-thirds of children with comorbid anxiety and depression experienced an anxiety disorder prior to their depression. Further, children with comorbid depression and anxiety experienced depression at a younger age compared to depressed children without comorbid anxiety (Kovacs et al. 1989).

Comorbidity of Anxiety with BPSD

Comorbid anxiety disorders are also common among youth with BPSD, with reported ranges of 44% to 77% (Harpold et al. 2005; Masi et al. 2001b; Sala et al. 2010). Youth with BPSD and comorbid anxiety had significantly longer duration of mood symptoms, higher depression scores, greater likelihood of familial depression, and high rates of BP-II compared to those without comorbid anxiety disorders. Comorbid anxiety disorders were not associated with severity of manic symptoms (Sala et al. 2010) but were associated with earlier age of onset of BP-I and more psychiatric hospitalizations (Dickstein et al. 2005).

Treatment Response

Despite the assumption that comorbidity may significantly impact treatment outcome for children with mood disorders, few studies have examined this empirically, although such knowledge could contribute to improved outcomes for children with comorbid mood and anxiety disorders (Emslie et al. 2003). Mediator and/or moderator relationships might exist. For example, perhaps children's mood symptoms only improve following improvement in anxiety symptoms (or vice versa), an example of a mediator relationship. On the other hand, perhaps children with comorbid anxiety disorders are less likely to respond to treatment for mood disorders, in which case the anxiety disorder would function as a treatment moderator.

Several studies discussed below have examined anxiety comorbidity as a potential treatment moderator.

Depression

Six major adolescent depression treatment studies have examined the role of comorbid anxiety on therapy outcome, three also included psychopharmacology. No studies have done so with children. In the Treatment for Adolescents with Depression Study (TADS), adolescents with comorbid anxiety disorders benefited less from acute intervention [fluoxetine, cognitive behavioral therapy (CBT), CBT+ fluoxetine, or clinical management + pill placebo], as measured by change in Children's Depression Rating Scale –Revised (CDRS-R; Poznanski et al. 1984) scores (Curry et al. 2006). In Brent and colleagues' 1998 comparison of CBT, systematic-behavioral family therapy (SFT) and nondirective supportive therapy (NST), comorbid anxiety predicted the presence of a MDD diagnosis at the end of acute treatment. Comorbidly anxious patients responded better to CBT than the other two treatments, perhaps due to shared cognitive distortions in depressive and anxiety disorders. While all three treatments did not have any acute effects on anxiety symptoms (Brent et al. 1998), by the 24-month follow-up, CBT and NST tended to be associated with a more consistent reduction in anxiety compared to SFT (Kolko et al. 2000). Finally, in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), 192 youth were treated with routine psychological care and psychopharmacology, with half also receiving CBT. Comorbid Obsessive Compulsive Disorder (OCD) specifically was associated with an increased risk of end-point depression at 28 week follow-up across conditions (Wilkinson et al. 2009).

In the Adolescent Coping with Depression Course (CWD-A), depressed adolescents with comorbidity, anxiety disorders in particular, entered the study more depressed and more functionally impaired than adolescents with depression and no comorbidity. While comorbid anxiety disorders had no impact on diagnostic recovery or recurrence of depressive disorders, they were associated with significantly greater reductions in Beck Depression Inventory (BDI) scores during treatment, a finding probably due to comorbidly anxious patients' higher pre-treatment depression scores (Rohde et al. 2001).

In a study of Interpersonal Psychotherapy for Depressed Adolescents (IPT-A), participants with comorbid anxiety disorders had more severe depression at study entrance. Post-treatment, adolescents with comorbid anxiety had higher depression scores but did not differ from those without comorbid anxiety regarding levels of functioning. Of 43 adolescents with an anxiety disorder, IPT-A was associated with significant reductions in depression compared with adolescents who received TAU; this finding was not detected in the 19 adolescents without comorbid anxiety. While IPT-A was not associated with significant decreases in anxiety, adolescents whose anxiety improved reported better overall functioning and fewer depressive symptoms compared with those whose anxiety did not improve (Young et al. 2006).

Asarnow and colleagues (2009) examined moderators of treatment response of the Treatment of Resistant Depression in Adolescents (TORDIA) study, which focused on second-step treatment strategies (either 12 weeks of a medication switch and CBT or a

medication switch alone) among adolescents with selective serotonin reuptake inhibitor (SSRI) treatment-resistant depression. CBT + medication change was superior to medication alone; in those with comorbid anxiety disorders (38.9%) this finding was amplified (Asarnow et al. 2009).

In sum, there was conflicting evidence regarding whether comorbidly depressed and anxious adolescents displayed a more robust treatment response than those with depression alone. When the former occurred, it appeared to be due to greater symptom severity in the comorbidly impaired group at baseline. In some studies, comorbid anxiety was associated with poorer treatment outcome. There was no evidence that depression treatments were effective in treating anxiety symptoms (other than CBT was more beneficial than SFT or NST).

Bipolar Disorder

No studies have evaluated the effect of comorbid anxiety symptoms on psychosocial treatments for children diagnosed with BPSD. In a naturalistic pharmacotherapy study, comparisons between youth treated with valproic acid (VPA) monotherapy and youth treated with VPA plus an adjunctive medication revealed that children with higher rates of comorbid anxiety, specifically, Generalized Anxiety Disorder (GAD), Separation Anxiety Disorder (SAD) and/or specific phobia were more likely to be maintained on VPA monotherapy. The authors suggest this might be due to greater symptom improvement due to the antianxiety effect of VPA (Masi et al. 2010). These data are encouraging, given that SSRIs, an efficacious medication for anxiety disorders (e.g. Walkup et al. 2008), may trigger manic or mixed episodes among children with BPSD, leaving prescribers few medication alternatives for comorbidly anxious patients (Kowatch et al. 2005). However, a study of 12-month outcome of adolescents following initial hospitalization for BPSD revealed comorbid anxiety disorders were associated with poorer recovery (DelBello et al. 2007).

Psychoeducational Psychotherapy

Current treatment guidelines for DSD and BPSD in children advocate for psychoeducation in addition to medication and psychotherapy (Hughes et al. 1999; McClellan et al. 2007). One type of psychotherapy, psychoeducational psychotherapy (PEP), contains three important components: education, support, and skill-building (Fristad et al. 2011). PEP, adjunctive to current treatment, teaches families about the symptoms of mood disorders as well as their biopsychosocial management. Children learn emotion regulation, communication and problem solving skills. Youth who received treatment with PEP administered in multi-family groups (MF-PEP) had a significantly greater decrease in mood severity index (MSI) scores at 12-month follow-up compared to waitlist controls who received treatment as usual during that time period (Fristad et al. 2009). Symptom improvement was maintained through the 18-month follow-up period for the immediate treatment group; the waitlist group experienced improvement similar to the immediate treatment group after receiving treatment between 12 and 18 months (Fristad et al. 2009). As over two-thirds of participants in the MF-PEP study had comorbid anxiety disorders, it is possible to examine the role anxiety disorders play in the treatment of these mood impaired children.

Current Study

MF-PEP meets the criteria (Silverman and Hinshaw 2008) of a “probably efficacious” adjunctive treatment to medication and psychotherapy for youth with BPSD (www.effectivechildtherapy.com) and has been shown to be similarly beneficial for children with depression (Fristad et al. 2009). Multiple MF-PEP treatment components might be beneficial in reducing both mood and anxiety symptoms. Nonetheless, the focus of MF-PEP is treating mood disorders. It lacks specific anxiety treatment components, such as somatic management training and exposure methods (Albano and Kendall 2002). Therefore, while it is hypothesized that MF-PEP may help reduce some symptoms of anxiety due to the greater impairment and complicated course evidenced by comorbid anxiety conditions (e.g. Sala et al. 2010), it is also hypothesized that comorbid anxiety will predict slower rates of improvement in mood. Of note, anxiety symptoms were common in the sample, even among participants who did not meet criteria for an anxiety diagnosis. Thus, analyses focused on anxiety symptoms rather than diagnoses.

Three hypotheses were examined: 1) the number of anxiety symptoms in the full sample would be positively correlated with depressive and manic symptom severity scores, but would be negatively correlated with measures of global functioning; 2) participation in MF-PEP would reduce the number of anxiety symptoms from baseline to 1-year follow-up in the immediate group compared to the waitlist control group; 3) more baseline anxiety symptoms would predict slower rates of improvement in manic symptoms, depressive symptoms, and global functioning.

Method

Participants

The detailed methodology of the larger MF-PEP study is described elsewhere (Fristad et al. 2009). One hundred sixty-five children with mood disorders participated (see Fig. 1). Participating families met four inclusion criteria: (1) the child was aged 8 to 11 years at baseline; (2) the child received a study diagnosis of a mood disorder (not adjustment disorder); (3) the child had a full-scale IQ score of 70 or higher; and (4) the child and one or more parents completed the baseline assessment and were willing to participate. Children were recruited from a variety of sources, including mental and physical health care providers (62%), local news stories (not advertisements; 19%), and word of mouth or fliers (19%). Families were willing to travel to the study, and 22% came from rural settings. The mean (SD) round trip was 56 (64) miles and ranged from two to 344 miles. The first 50 families were referrals from therapists and parents who attended a local evening program and/or full day workshop on treating bipolar disorder in youth. Due to this strong response from families who reported difficulty finding therapy for pediatric bipolar disorder, BPSD was more highly represented in the sample than DSD.

Each child had one or two parents, legal guardians and/or caregivers (hereafter referred to as “parents”) who participated in assessments (all interested parents were invited to participate in treatment). When two parents in a family completed assessments, one self-selected to be the primary informant and the other served as the secondary informant. Families were

recruited in 11 sets of 15 each; a set was recruited every 3 months. Within each family set, seven families were randomized into immediate treatment (IMM) and eight families were randomized into a 1-year wait-list control group condition (WLC). One family was erroneously assigned to IMM who should have been in WLC, resulting in 78 IMM families and 87 WLC families. All families received treatment-as-usual (TAU) throughout the study (i.e., they were encouraged to continue receiving any existing mental health or school-based services throughout the 18-month study, and to make any changes to their treatment they felt were warranted).

At study entry, child participants were aged 8 to 11 ($M=9.9$, $SD=1.3$); parents' mean age was 40.8 ($SD=7.8$). Most (90.9%) children were White, Non-Hispanic; 6.7% of the children were African American; 1.8% were mixed race; and 0.6% were White, Hispanic. A majority (73%) were male. The children's IQ, estimated by the Kaufman Brief Intelligence Test (K-BIT), ranged from 71 to 148 ($M=106.9$, $SD=14.9$). Median family income was \$40,000 to \$59,000 per year and ranged from less than \$20,000 to over \$100,000. All child participants were diagnosed with an Axis I mood disorder; most (70%, $n=115$) had a BPSD. The remainder (30%, $n=50$) were diagnosed with a DSD. Specific diagnoses in declining frequency included: BP-I ($n=62$; 37.5%); MDD ($n=38$, 23%); BP-NOS ($n=29$, 17.5%); BP-II ($n=22$; 13.3%); MDD/DD ($n=6$); DD ($n=5$); Substance-Induced Mood Disorder ($n=1$ within BP spectrum; $n=1$ within depressive spectrum); and Mood Disorder-NOS ($n=1$). All participants had at least one comorbid diagnosis. Most (97%) were diagnosed with a comorbid behavioral disorder; 69% of the participants were diagnosed with a comorbid anxiety disorder.

Measures

The *Children's Interview for Psychiatric Syndromes—Child and Parent Forms* (ChIPS, P-ChIPS; Weller et al. 1999a, b) were administered to each child and primary informant parent to determine study diagnosis and comorbid disorders upon entry and at 1-year followup. ChIPS screens for 20 Axis I disorders and psychosocial stressors, and is based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Specific anxiety disorders assessed include: specific phobia, social phobia, SAD, GAD, OCD, Acute Stress Disorder (ASD) and Post Traumatic Stress Disorder (PTSD). Its reliability and validity as a diagnostic instrument in clinical research has been demonstrated in child and adolescent samples (Weller et al. 2000). Inter-rater reliabilities for the ChIPS and P-ChIPS were substantial ($\kappa=0.82$ and 0.78 , respectively, based on diagnosis agreement).

Besides providing information about the number and types of diagnoses, ChIPS also provided information about number and types of symptoms endorsed. To create a continuous measure of anxiety symptoms, the BAMO (Behavior, Anxiety, Mood, Other) technique (Cerel and Fristad 2001) was applied. For each disorder, the number of symptoms was divided by the total number of possible symptoms for that disorder on P-ChIPS and ChIPS. This technique created standardized numbers, between zero and one, allowing for comparison between disorders. These scores were then summed across all the anxiety disorders to create an index score for anxiety symptoms. This allowed for analyses of dimensional (symptom) data (Cerel and Fristad 2001). The BAMO technique has been

shown to correlate highly with other psychopathology measures and to successfully discriminate between known groups (Cerel and Fristad 2001). BAMO-Anxiety scores were created for parent and child ratings on P-ChIPS and ChIPS, respectively.

The CDRS-R (Poznanski et al. 1984) and the Young Mania Rating Scale (YMRS; Young et al. 1978) were administered to each parent and child upon study entry and at each follow-up. The CDRS-R is conducted in interview format and assesses the severity of 17 depressive symptoms. It has demonstrated good psychometric properties, showing adequate reliability and validity (Poznanski et al. 1984). The YMRS is an 11-item interview that assesses severity of manic symptoms and also has demonstrated good psychometric properties (Double 1990; Fristad et al. 1992, 1995; Youngstrom et al. 2002). Inter-rater reliability for the YMRS and CDRS-R was substantial [κ (score ± 1) = 0.71 and 0.68, respectively].

The *Children's Global Assessment Scale (C-GAS)* is a clinician rating of global functioning based on assessment of a child's school, home, and peers. Scores range from one (indicating severely impaired functioning) to 100 (indicating superior functioning) (Shaffer et al. 1983). Two clinical psychologists (masked to group status) separately reviewed reports then held a consensus meeting to arrive at one C-GAS score. The C-GAS was completed upon study entry and at each follow-up. Inter-rater reliability (score ± 5) was substantial (κ = 0.68).

Procedures

All assessments and MF-PEP group sessions occurred at a Midwestern university medical center as part of a larger trial (National Institute of Mental Health #R01MH061512). Trained interviewers, including clinical child psychology graduate students and postdoctoral trainees, administered assessments. Interviewers were masked to participant treatment status. Interviewer training included didactics, followed by rating mock, videotaped, and live interviews. After establishing reliability (κ = 0.70) on training interviews, interviewers were videotaped performing live interviews. These interviews were coded by the postdoctoral project coordinator. Interviewers could conduct interviews independently after establishing reliability (κ = 0.70) at this step. To maintain reliability, 10% of all interviews were videotaped.

Each primary parent participant completed phone pre-screening to determine if the child likely met diagnostic criteria for a mood disorder and if the child lived with one or more parent. If so, the family was scheduled for a baseline assessment. Prior to completion, children and parents provided written informed assent and consent and completed Health Insurance Portability and Accountability Act documentation (if enrolled after these procedures were initiated), as approved by the Institutional Review Board. Families received payment for assessments, but not therapy sessions. Free parking and sibling childcare was provided to families at each session.

After the baseline assessment, the assessment team, including the principal investigator, project coordinator, and parent and child interviewers, met within 48 h to determine study eligibility and diagnostic category (i.e., BPSD or DSD). Study eligibility and diagnostic category were determined based on the information described above, except when there

were obvious reasons to disregard information from one informant (e.g., a child refused to answer questions seriously or a parent clearly provided exaggerated responses).

Stratified randomization was used after each set of 15 families completed their baseline assessments. Randomization was balanced to ensure that no group had only one member with a BPSD or DSD or only one girl and that IMM and WLC groups had approximately equal distributions of mood diagnostic category, comorbid conditions (i.e., behavior disorders-present/absent; anxiety disorders-present/absent), and demographic characteristics. The project coordinator summarized these variables and the principal investigator (who was masked to other information) completed randomization. Within each set, seven families were assigned to immediate treatment and eight were assigned to WLC. Subsequently, interviewers prepared a report summarizing their findings that was reviewed by two clinical researchers, both licensed psychologists experienced in childhood mood disorders, at which time a precise diagnosis (e.g., BP-I, MDD) was given.

Treatment

MF-PEP consisted of eight 90-min sessions that began and ended with parents and children together (typically five to eight families per group). The majority of each session was held separately for parents and children. The child group was led by a group leader (a post-doctoral trainee or advanced level graduate student) and co-leader (an advanced level graduate student). Each session covered a specific topic. While no session was devoted strictly to anxiety comorbidity or its specific treatment, comorbidity was discussed throughout group sessions.

Each session began with a check-in meeting of parents and children, at which time they discussed projects assigned and issues from the previous week. Parent and child groups then separated to complete their particular goals, topics, and activities. After their “lesson of the day,” children received 15 to 20 min of social skills training via noncompetitive group recreational activities. At the end of each session, children rejoined their parents to discuss what they learned and their upcoming family projects (Fristad et al. 2011).

Although discussed in the context of mood disorders, many parent session components provide general skills that may be helpful for anxiety disorders as well. These include: 1) learning to manage and track their child’s medications; 2) learning to manage school and mental health systems of care; 3) building symptom management techniques and coping skills. As children with comorbid mood and anxiety disorders have complex treatment needs and frequently have academic impairment, each of these treatment components could potentially alleviate some of the child’s anxiety symptoms, in addition to their mood symptoms. Likewise, several child session components might be beneficial in treating anxiety symptoms, including: 1) identifying feelings; 2) improving emotion regulation; 3) increasing social skills; and 4) improving communication skills and problem solving capacity.

Treatment-As-Usual

TAU was assessed using the Service Provider and Medication Usage Grids (Mendenhall et al. 2010) and is described in more detail elsewhere (see Cummings and Fristad 2007;

Mendenhall 2007; Mendenhall et al. 2009). In brief, children and their families utilized an average of 2.58 services at baseline ($SD=1.41$; range=0–7). Services most commonly used were psychiatrists (68%), school services (43%), psychologists (38.8%) and therapists (non-psychologists; 38.2%; Mendenhall 2007). Pharmacotherapy was the most frequently used treatment (82%), with children prescribed an average of 2.3 psychotropic medications ($SD=1.5$; range=0–7; Cummings and Fristad 2007). MF-PEP was hypothesized to help families take a more active role in their child's treatment; learning to manage multiple medications and systems of care was a key ingredient. Findings indicated that participation in MF-PEP not only improved service utilization by participating families in IMM compared with WLC, but that effect mediated improvements in mood severity scores as a result of treatment (Mendenhall et al. 2009). Additionally, variance in the number of medications taken by the sample decreased from pre- to post-treatment (Cummings and Fristad 2007).

Missing Data

Missing data were not common in this study and appeared to occur mostly at random. The largest amount of missing data was found with child YMRS and CDRS-R ratings. If a child was unwilling or reluctant to answer questions, or if a child's responses on these measures were considered unreliable, that child's responses were considered missing. Child-reported data for the CDRS-R were missing for no participants at baseline, four participants at Time 2, and seven participants at Time 3. Child-reported data for the YMRS were missing for two participants at baseline, five participants at Time 2, and four participants at Time 3. At Time 2, 21 participants were lost to attrition, at Time 3, 22 participants were lost, and at Time 4, 13 participants were lost. Symptoms of depression, mania, or anxiety were not significantly associated with attrition rates. Children who did not complete all four assessments had significantly poorer functioning (C-GAS scores) at baseline compared to children who attended all assessments.

Results

Parent and Child Report

Although all analyses were conducted on both parent- and child-report data, results did not differ in terms of statistical significance between the two sets of analyses. For the purpose of brevity, only analyses from the parent data are reported below.

Sample Description

Children in the IMM and WLC groups did not differ on the following baseline variables: C-GAS scores [$F(1,163)=1.19$, $p=0.28$], CDRS-R ratings [$F(1,163)=0.00$, $p=0.97$], and YMRS ratings [$F(1,163)=0.64$, $p=.42$]. See Table 1.

Participants had a mean number of 1.4 anxiety disorders: 31.5% had no anxiety disorder; 29.7% had one anxiety disorder; 15.2% had two anxiety disorders; 18.8% had three anxiety disorders; 3.6% had four anxiety disorders; and 1.2% had five anxiety disorders. Overall number of anxiety disorders did not differ between the DSD and BPSD groups [independent t -test, DSD ($M=1.3$) versus BPSD ($M=1.4$) groups, $t(163)=0.33$, $p<0.74$]. Pearson chi-square analyses revealed no differences in frequency of specific anxiety disorders for the

DSD and BPSD groups (see Table 2). In the full sample, 42.4% had specific phobia, 41.8% had GAD, 33.3% had SAD, 13.3% had social phobia, and 3.0% each had OCD and PTSD.

Correlations of Anxiety and Mood Symptoms and Functional Impairment

Pearson correlation coefficients (see Table 3) were calculated for the entire baseline sample to assess the strength of relationship between anxiety symptoms (BAMO-Anxiety), CDRS-R ratings, YMRS ratings, and C-GAS scores. As hypothesized, BAMO-Anxiety scores were significantly positively correlated with CDRS-R ratings and significantly negatively correlated with C-GAS scores. BAMO-Anxiety scores were not correlated with YMRS ratings.

Impact of MF-PEP on Anxiety Symptoms

Analysis of covariance (ANCOVA) was used to determine if participation in MF-PEP would reduce the number of anxiety symptoms from baseline to 1-year follow-up in the IMM compared to the WLC group. The number of anxiety symptoms (BAMO-Anxiety scores) at Time 3 in the IMM group ($M=1.34$, $SD=1.53$) was compared to the WLC group ($M=1.40$, $SD=1.34$) using baseline BAMO-Anxiety scores for the IMM group ($M=1.47$, $SD=1.41$) and WLC ($M=1.27$, $SD=1.30$) as covariates. Contrary to hypotheses, 1-year follow-up BAMO-Anxiety scores did not differ between the IMM and WLC groups after covarying baseline BAMO-Anxiety scores, $F(1,120)=0.25$, $p=0.62$ (see Table 4). Thus, participation in MF-PEP does not appear to significantly impact anxiety symptoms.

Impact of Anxiety Symptoms on Treatment Outcome

Linear mixed effects (LME) procedures were used to determine if more anxiety symptoms at baseline would predict slower rates of improvement in manic symptoms, depressive symptoms, and global functioning over times 1, 2, and 3. Baseline BAMO-Anxiety scores were added to the model as a covariate. Contrary to hypotheses, baseline BAMO-Anxiety scores did not impact improvement in mood [YMRS scores, $F(1, 307.24)=0.01$, $p=.94$; CDRS-R scores, $F(1, 301.14)=0.11$, $p=0.74$ in IMM compared to WLC over time]. For the C-GAS, however, a significant 3-way interaction occurred between BAMO-Anxiety scores, treatment group, and timepoint [C-GAS scores, $F(1, 303.40)=5.55$, $p=0.02$]. Based on the definition of a moderator as proposed by Baron and Kenny (1986) (i.e., an interaction between an independent variable and a third variable), baseline anxiety was a moderator in the current analyses. However, this association was opposite the hypothesized direction. More baseline anxiety symptoms were associated with greater improvement in global functioning over time for the IMM group.

Post Hoc Analyses

Analyses were re-run in two subsamples by mood diagnosis. In the BPSD group, results did not differ from the main findings discussed above. In the DSD group, trends remained in the same direction; however, findings that had achieved statistical significance were no longer significant. This likely occurred due to the reduced statistical power resulting from the small sample size of DSD children ($n=50$).

Discussion

Prevalence Rates

Comorbid anxiety disorders were common in this sample of 8- to 11-year-old children with mood disorders. Approximately one-third of participants presented with no comorbid anxiety disorders, nearly one-third of participants presented with one comorbid anxiety disorder, and just over one-third presented with more than one comorbid anxiety disorder. Children with DSD and BPSD did not differ in the overall number or specific type of anxiety disorders experienced. The two most common comorbid anxiety disorders were specific phobia and GAD. OCD and PTSD were the least common anxiety diagnoses. Prevalence estimates from the current study are similar to those reported in the previous literature (Dickstein et al. 2005; Harpold et al. 2005; Masi et al. 2007; Wilens et al. 2003; Yorbik et al. 2004).

Relationship between Anxiety Symptoms, Mood Symptoms, and Global Functioning

As expected, increased anxiety symptoms were associated with poorer global functioning. Interestingly, the correlation between depressive symptom severity and anxiety symptoms was significant, but not as high as anticipated based on the well-documented, strong relationship between depressive and anxious symptoms in youth community samples (Cole et al. 1998; Hale et al. 2009). To our knowledge, no other studies have examined the correlation of depressed and anxious symptoms in a clinical sample with psychopathology as severe as the MF-PEP sample. These findings could be due to the high rate of BPSD in our sample, or they could also be due to differences between the BAMO measure and those utilized in other trials. Future research regarding the relationship between depression and anxiety at the symptom level in both DSD and BPSD is needed.

The finding of no association between anxious and manic symptoms was contrary to our hypothesis. No studies have examined the impact of anxiety symptoms on manic symptoms, and studies examining anxiety diagnoses have yield mixed results. Previous data suggest comorbid anxiety diagnoses predicted: earlier age of onset in children (Dickstein et al. 2005) and adults (Simon et al. 2004); more psychiatric hospitalizations in children (Dickstein et al. 2005); and dramatically fewer days of euthymia, increased risk of relapse, and poorer quality of life in adults (Simon et al. 2004). Additional studies have found results consistent with our hypotheses (Birmaher et al. 2002; Sala et al. 2010). In MF-PEP participants, anxiety symptoms may have had negative associations with course of illness and depressive symptoms, but not with increased severity of symptoms measured on the YMRS.

Effect of MF-PEP on Anxiety Symptoms

Current treatment guidelines for mood disorders recommend focusing first on mood stabilization, followed by addressing comorbid symptoms (Hughes et al. 1999; Kowatch et al. 2005; McClellan et al. 2007). The current study hypothesized that MF-PEP would lead to a reduced number of anxiety symptoms. While the number of anxiety symptoms decreased for IMM participants and increased for WLC over time, this difference did not achieve statistical significance. Children with comorbid anxiety still appear to require treatment in addition to MF-PEP to specifically target their anxiety, particularly exposure-based CBT,

given exposure has been identified as a key component for the treatment of anxiety (e.g. Bouchard et al. 2004; Kendall et al. 1997; Kendall et al. 2005).

The few studies that have examined the effect of treatment for mood disorders on anxiety symptoms have found similar results (Kolko et al. 2000; Young et al. 2006). On the contrary, in two separate studies, CBT for children with anxiety led to reductions in both anxiety (Revised Children's Manifest Anxiety Scale; RCMAS) and depressive symptoms (Children's Depression Inventory; CDI), so it is possible that the reverse may be true (i.e., anxiety treatments may reduce both depressive and anxious symptoms; Kendall et al. 1997; Mendlowitz et al. 1999). However, in both studies, although all children met DSM-IV-TR criteria for one or more anxiety disorders, few children met criteria for a comorbid depressive disorder, and CDI scores revealed only low levels of depressive symptoms (Mendlowitz et al. 1999; Kendall et al. 1997).

Impact of Anxiety Symptoms on Mood Reduction following MF-PEP

Finally, the impact of comorbid anxiety symptoms on treatment was examined. It was hypothesized that comorbid anxiety disorders would complicate treatment such that children with comorbid anxiety diagnoses would show slower improvements in global functioning, manic symptom severity, and depressive symptom severity. Contrary to hypotheses, the number of anxiety symptoms did not impact improvement in manic or depressive symptom severity. Thus, it appears that MF-PEP is similarly effective in reducing depressive and manic symptom severity for participants regardless of anxiety symptomatology. This is important to note, as the majority of youth with mood disorders also experience anxiety symptoms.

These findings are inconsistent with previous research suggesting anxiety comorbidity predicts higher depression post-treatment (Brent et al. 1998; Curry et al. 2006; Wilkinson et al. 2009; Young et al. 2006) and a longer time to remission among BPD adults (Feske et al. 2000). Current positive results suggest MF-PEP appears successful in addressing the first step of treatment guidelines (i.e., stabilize the child's mood symptoms) (Hughes et al. 1999, 2007; Kowatch et al. 2005; McClellan et al. 2007), even among children with anxiety. Comparisons between previous findings and current results are difficult, given a variety of differences regarding sample characteristics (age, severity of psychopathology) and treatment conditions [psychoeducational psychotherapy + TAU versus individual therapy and, at times, psychopharmacology conditions]. Future research will inform generalizability of these findings.

Results differed from expected when the impact of anxiety symptoms on global functioning was examined. Children with more anxiety symptoms at baseline experienced greater improvements in C-GAS scores as a result of participating in MF-PEP, suggesting anxiety symptomatology at baseline moderated the impact of treatment on global functioning.

Three previous studies also demonstrate improved treatment response among depressed youth with comorbid anxiety disorders, suggesting comorbid anxiety symptoms may magnify treatment effects (Asarnow et al. 2009; Brent et al. 1998; Rohde et al. 2001; Young et al. 2006), perhaps due to the more severe depressive symptoms at baseline among this

group. CBT strategies may be particularly beneficial to youth with anxiety and depression, which may lead to greater improvements (Asarnow et al. 2009). However, improved treatment response among youth with comorbid anxiety is less documented in the pediatric BPSD literature, perhaps due to the paucity of research on this topic (Joshi and Wilens 2009). One study suggests anxiety comorbidity was associated with greater response to monotherapy (Masi et al. 2010), while another suggests comorbid anxiety predicted poorer recovery rates post-hospitalization for BPSD (DelBello et al. 2007). These findings, combined with findings of the current study, suggest further research on this topic is warranted.

In regards to the MF-PEP sample, several possible factors may have caused participants with more anxiety symptoms to make further improvements in their overall functioning compared to participants without comorbid anxiety. First, participants with comorbid anxiety symptoms may be able to apply the behavioral strategies taught by MF-PEP to their anxiety disorder as well, and may consequently experience greater improvements in functioning. As children with anxiety disorders often experience significant social skill deficits (Kendall et al. 1992), perhaps the emphasis MF-PEP placed on social skill building at each session was particularly helpful for this group in improving functioning, even if anxiety symptoms, per se, did not abate. Further, one of the goals of MF-PEP is to help families become better consumers of care; perhaps this was especially beneficial for children who began treatment with higher anxiety symptomatology and may present with more complex treatment concerns.

Finally, greater anxiety symptomatology was associated with more impairment in baseline functioning. Lower C-GAS scores provided these participants more room to improve. Once implementing MF-PEP strategies, these participants were able to narrow the gap between their baseline and potential level of functioning. Participants with less functional impairment may have had fewer improvements to make and thus showed less improvement in global functioning.

Limitations

The current study had several limitations. First, randomization into IMM and WLC was completed by PI assignment to ensure relatively equal therapy group composition. Although IMM and WLC did not differ on key baseline characteristics, this must be considered when interpreting findings. Second, many analyses were conducted, increasing the chances of Type I error. Due to the exploratory nature of this study, statistical correction was not applied. This should be taken into account when considering analyses that achieved statistical significance. Further, the focus of the larger study was to examine the effect of MF-PEP on childhood mood disorders. Thus, questionnaires specifically targeting anxiety symptoms, such as the Multidimensional Anxiety Scale for Children (MASC; March et al. 1997) or the Anxiety Disorders Interview Schedule for Children (ADIS-C/P; Silverman and Albano 1996) were not included. The range of the measure used (BAMO) was restricted, so findings may have differed with an alternate measure. Moreover, comorbid symptoms may have been over-represented in participants compared to the general population, because individuals who suffer from multiple conditions are more likely to seek treatment (Berkson

1946). Almost all MF-PEP participants (97%) presented with a comorbid behavioral disorder. However, comorbidity is the rule, not the exception in childhood mood disorders, and behavioral disorders have been described as universally high among children with mood disorders (Kowatch et al. 2005; Joshi and Wilens 2009; Sachs et al. 2000). Thus, treating a child with comorbid anxiety, behavior, and mood disorders is not an uncommon experience.

Clinical Implications and Future Directions

This study has several important clinical implications. First, anxiety comorbidity appears prevalent among children with bipolar and depressive disorders. Treatment guidelines suggest clinicians should carefully assess for comorbidity (Birmaher et al. 2007; Hughes et al. 2007; Kowatch et al. 2005). Anxiety symptoms are associated with significant, negative effects on children with mood disorders (i.e. greater depressive symptom severity, poorer global functioning), and clinicians should assess and monitor these symptoms over time.

Current pediatric bipolar treatment guidelines suggest clinicians should first work to stabilize the patient's mood (Kowatch et al. 2005). Among depressed youth with comorbidities, clinicians are instructed to first treat whichever disorder is causing greater distress and impairment (Birmaher et al. 2007). The current findings suggest that MF-PEP may be particularly helpful in improving global functioning among children with higher levels of baseline anxiety symptoms. Families of children with a mood diagnosis and comorbid anxiety symptoms may especially benefit from education about both disorders and how to coordinate more complex medication regimens and systems of care. However, MF-PEP does not effectively reduce anxiety symptoms. After mood symptoms have been stabilized, children will still require implementation of strategies proven effective in previous literature, such as exposure-based CBT. Clinicians who work with mood disordered children need to flexibly implement evidence-based treatments as they address frequently occurring comorbidities.

This study was unique regarding its severity of psychopathology, younger age of participants, and psychoeducational psychotherapy + TAU treatment approach. Current findings call for further research to assess the effect of comorbidity on treatments for children with mood and anxiety disorders. Although anxiety did not impact treatment outcome, the specific mechanisms through which anxiety may impact treatment have not been elucidated. Finally, recent efforts have examined transdiagnostic CBT approaches for mood and anxiety disorders (Wilamowska et al. 2010). The field may benefit from continued efforts to develop combination treatments tailored to address the complex needs of children with a variety of comorbid diagnoses.

Acknowledgments

This article was written with the support of the National Institute of Mental Health Grant R01MH061512. The data presented in this paper are from a doctoral dissertation prepared by the first author, titled "The Impact of Comorbid Anxiety on Treatment Outcome of a Family-Based Psychoeducational Psychotherapy Program for Children with Mood Disorders."

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Fig. 1.
Participant flow chart for the Multi-Family Psychoeducational Psychotherapy randomized trial

Table 1

Mean depression, manic, anxiety and global functioning ratings in the immediate and wait-list control groups

Measure	Immediate group			Wait-list control group		
	M	SD	Range	M	SD	Range
CDRS-R	40.03	13.05	21–84	40.11	14.06	19–81
YMRS	21.29	10.38	3–47	19.95	11.01	1–47
BAMO-A	1.47	1.41	0–6.11	1.26	1.30	0–5.78
C-GAS	42.99	8.00	18–60	44.41	8.75	17–60

CDRS-R Children's Depression Rating Scale-Revised ratings; YMRS Young Mania Rating Scale ratings; BAMO-A BAMO-Anxiety scores; C-GAS Children's Global Assessment Scale

Table 2

Prevalence (%) of anxiety disorders among participants with depressive spectrum disorder (DSD) versus bipolar spectrum disorder (BPSD)

Anxiety Disorder	DSD	BPSD	χ^2 (1)	<i>P</i>
Specific Phobia	48.0	40.0	0.91	0.34
GAD	38.0	43.5	0.43	0.51
SAD	26.0	36.5	1.74	0.19
Social Phobia	14.0	13.0	0.03	0.87
OCD	4.0	2.6	0.23	0.63
PTSD	2.0	3.5	0.26	0.61

GAD generalized anxiety disorder; *SAD* separation anxiety disorder; *OCD* obsessive-compulsive disorder; *PTSD* post-traumatic stress disorder

Table 3

Pearson correlations of depressive, manic, anxiety and global functioning ratings

	1	2	3	4
1. CDRS-R	–	0.30**	0.17*	–0.33**
2. YMRS		–	–0.04	–0.44**
3. BAMO–A			–	–0.30**
4. C-GAS				–

CDRS-R Children's Depression Rating Scale-Revised ratings; *YMRS* Young Mania Rating Scale ratings; *BAMO-A* BAMO-Anxiety scores; *C-GAS* Children's Global Assessment Scale

**
 $p < 0.01$.

*
 $p < 0.05$

Table 4

Analysis of covariance (ANCOVA) of anxiety symptoms as a function of treatment

Group	Time 1	Time 2	ANCOVA	
	<i>M (SD)</i>	<i>M (SD)</i>	<i>F (1, 120)</i>	<i>d</i>
Immediate treatment	1.47 (1.41)	1.34 (1.53)	0.25	0.08
Waitlist control	1.27 (1.30)	1.40 (1.34)		