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Mediators in the randomized trial of Child- and Family-Focused Cognitive-Behavioral Therapy for pediatric bipolar disorder

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ABSTRACT

Mediation analyses can identify mechanisms of change in Cognitive-Behavioral Therapy (CBT). However, few studies have analyzed mediators of CBT for youth internalizing disorders; only one trial evaluated treatment mechanisms for youth with mixed mood diagnoses. This study evaluated mediators in the randomized trial of Child- and Family-Focused CBT (CFF-CBT) versus Treatment As Usual (TAU) for pediatric bipolar disorder (PBD), adjunctive to pharmacotherapy. Sixty-nine children ages 7–13 with PBD were randomly assigned to CFF-CBT or TAU. Primary outcomes (child mood, functioning) and candidate mediators (family functioning, parent/child coping) were assessed at baseline and 4-, 8-, 12- (post-treatment), and 39-weeks (follow-up). Compared with TAU, children receiving CFF-CBT exhibited greater improvement in mania, depression, and global functioning. Several parent and family factors significantly improved in response to CFF-CBT versus TAU, and were associated with the CFF-CBT treatment effect. Specifically, parenting skills and coping, family flexibility, and family positive reframing showed promise as mediators of child mood symptoms and global functioning. Main or mediating effects for youth coping were not significant. CFF-CBT may impact children's mood and functioning by improving parenting skills and coping, family flexibility, and family positive reframing. Findings highlight the importance of parent coping and family functioning in the treatment of PBD.

1. Introduction

1.1. Pediatric bipolar disorder

There is much controversy surrounding the diagnosis of pediatric bipolar disorder (PBD). According to a recent meta-analysis of epidemiological studies, the mean prevalence of PBD is 1.8% when employing broad definitions (including bipolar I and II disorders, cyclothymia, and other specified/unspecified bipolar and related disorders; Van Meter, Moreira, & Youngstrom, 2011). However, rates are lower when using narrow criteria (1.2% for bipolar I disorder) and higher among older samples (2.7% for PBD in youth ≥ 12 years; Van Meter et al., 2011). Thus, while bipolar disorder is more common in adolescents, it can also onset in prepubertal children, who often initially present with sub-syndromal forms of PBD (cyclothymia and other specified/unspecified bipolar and related disorders), but with comparable symptom severity and functional impairment as youth with bipolar I disorder (Hafeman et al., 2013).

Although the diagnostic criteria for bipolar disorder are the same in children and adults, the clinical presentation varies across the lifespan. The most common symptoms of pediatric mania include increased energy, irritability, and mood lability (Van Meter, Burke, Kowatch, Findling, & Youngstrom, 2016). Compared to adults with bipolar disorder, children and adolescents with PBD spend more time symptomatic with mixed presentations, rapid mood fluctuations, and subthreshold symptoms (Birmaher et al., 2009; Geller, Tillman, Bolhofner, & Zimerman, 2008), and have greater impairment in functioning and quality of life (Perlis et al., 2009). In addition, youth with PBD often present with: psychotic features and psychiatric comorbidity, especially with attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (Birmaher et al., 2009; Geller et al., 2008; Van Meter et al., 2016); poor psychosocial and family functioning (Keenan-Miller, Peris, Axelson, Kowatch, & Miklowitz, 2012; Kim, Miklowitz, Biuckians, & Mullen, 2007; Nader et al., 2013); and suicidality (Hauser, Galling, & Correll, 2013).

Given the considerable morbidity associated with PBD, research has sought to identify efficacious treatments. While pharmacotherapy is often an essential component of the regimen (McClellan,

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Kowatch, Findling, & the Work Group on Quality Issues, 2007; Pavuluri et al., 2004b), psychosocial interventions are also important for teaching families about symptoms and course of PBD and fostering symptom management skills, such as affect regulation, problem solving, and effective communication (Fristad & MacPherson, 2014; Weinstein, West, & Pavuluri, 2013). Currently, approaches that incorporate family-focused psychoeducation and Cognitive-Behavioral Therapy (CBT) have the most empirical support (Fristad & MacPherson, 2014). Efficacy of these psychosocial interventions has been demonstrated in four large, rigorous randomized controlled trials (RCTs): Family-Focused Treatment + pha rmacotherapy versus brief psychoeducation + pharmacotherapy (Miklowitz et al., 2008, 2013); Multi-Family Psychoeducational Psychotherapy (MF-PEP) + Treatment As Usual (TAU) versus waitlist control (WLC) + TAU (Fristad, Verducci, Walters, & Young, 2009); and Child- and Family-Focused CBT (CFF-CBT) + pharmacotherapy versus enhanced TAU + pharmacotherapy (West et al., 2014). Of these treatments, only MF-PEP and CFF-CBT have been tested exclusively with school-aged children; the original RCT of FFT included predominantly adolescents (Miklowitz et al., 2008), while the second trial of FFT for youth at high risk for bipolar disorder included both younger children and adolescents (Miklowitz et al., 2013).

1.2. Mediators of Cognitive-Behavioral Therapy for youth internalizing disorders

Though RCTs are the gold standard for determining efficacy, moderator and mediator analyses are also important for discerning subgroups for whom treatments may be more or less effective and mechanisms of change, respectively (Kraemer, Wilson, Fairburn, & Agras, 2002). Such factors can offer an empirical basis for matching patients to interventions, identifying treatment targets, and elucidating components associated with outcomes (Weersing & Weisz, 2002). In the adult depression psychotherapy literature, many studies have focused on the temporal relationship between in-session behaviors (e.g., therapist adherence, alliance, and cognitive strategies), reappraisal, and treatment-related symptom change (e.g., Lorenzo-Luaces, German, & DeRubeis, 2015). Indeed, the strongest evidence for mediation occurs when therapeutic procedures lead to changes in mediators, prior to changes in outcomes (Kraemer et al., 2002).

While comparatively less attention has been paid to mechanisms of CBT for youth internalizing disorders (Webb, Auerbach, & DeRubeis, 2012), several potential mediators have been identified. Specifically, CBT for pediatric anxiety may affect change by: reducing children's negative/anxious self-statements; increasing children's perceived control, positive self-statements, and coping strategies; and improving family functioning and strain (Hogendoorn et al., 2014; Kendall et al., 2016; Kendall & Treadwell, 2007; Schleider et al., 2015; Treadwell & Kendall, 1996). Potential mediators of CBT for adolescent depression include: reducing youths' cognitive distortions, automatic negative cognitions, and cognitive avoidance; and improving youths' positive outlook and engagement in pleasant activities (Jacobs et al., 2014; Kaufman, Rohde, Seeley, Clarke, & Stice, 2005; Kolko, Brent, Baugher, Bridge, & Birmaher, 2000; Stice, Rohde, Seeley, & Gau, 2010). Improvements in positive parenting, parental emotional reactions, and maternal depression may also mediate depression reduction in preventive interventions for younger, at-risk children (Compas et al., 2010; DeGarmo, Patterson, & Forgatch, 2004) and CBT for traumatized youth (Holt, Jensen, & Wentzel-Larsen, 2014).

Despite growing research on mechanisms of change in CBT for internalizing disorders, only one trial has evaluated mediators of a psychosocial intervention for youth with PBD or depression. In the RCT of MF-PEP + TAU versus WLC + TAU, improvement in quality of mental health service utilization was mediated by parents' positive beliefs about treatment, and improvement in children's mood symptoms was mediated by quality of services used (Mendenhall, Fristad, & Early, 2009). Thus, MF-PEP helped parents become better mental health consumers and advocates, and access to higher-quality services resulted in children's decreased symptom severity (Fristad et al., 2009). Although not yet studied, it is also expected that improvements in parenting skills and coping, family functioning, and the home environment would facilitate children's symptom improvement, as these deficits are associated with PBD in cross-sectional studies (Keenan-Miller et al., 2012; Nader et al., 2013; Schenkel, West, Harral, Patel, & Pavuluri, 2008), predictive of worse course in longitudinal analyses (Geller et al., 2008; Kim et al., 2007; Sullivan, Judd, Axelson, & Miklowitz, 2012), and thus directly targeted in Evidence-Based Treatments (EBTs) for PBD (Fristad & MacPherson, 2014; Weinstein et al., 2013).

1.3. Child- and Family-Focused Cognitive-Behavioral Therapy for pediatric bipolar disorder

Given limited research on mediators of EBTs for PBD, this study analyzed mechanisms of change in the RCT of CFF-CBT (West et al., 2014). This comprehensive, family-based intervention integrates CBT with psychoeducation and complementary mindfulness and interpersonal/family therapy techniques. The theoretical framework underlying CFF-CBT considers dysfunctions commonly observed in PBD, including: developmental manifestations of PBD (e.g. mixed mood states, rapid mood fluctuations, psychosis, and comorbidity; Birmaher et al., 2009; Geller et al., 2008); affective circuitry brain dysfunction (e.g. poor problem-solving during affective stimulation via hypoactivation of the dorsolateral and ventrolateral prefrontal cortices, hyperactivation of the amygdala, and deficits in the superior temporal and visual cortices: Garrett et al., 2012; Passarotti & Pavuluri, 2011); and impairment in psychosocial and family functioning (Keenan-Miller et al., 2012; Kim et al., 2007; Nader et al., 2013; Schenkel et al., 2008).

Specifically, the 12 acute and 6 maintenance sessions of CFF-CBT teach children, parents, and families coping skills comprising the treatment acronym, “RAINBOW,” including: **R**outine (development of consistent daily routines); **A**ffect Regulation (psychoeducation about emotions; mood monitoring; coping strategies to enhance mood regulation); **I** Can Do It! (improvement in child self-esteem and parent self-efficacy); **N**o Negative Thoughts/Live in the **N**ow (cognitive restructuring and mindfulness to reduce negative thoughts); **B**e a Good Friend/**B**alanced Lifestyle (social skill-building and parent self-care); **O**h How Do We Solve this Problem? (family problem-solving and communication training); and **W**ays to Find Support (enhanced support networks; Pavuluri et al., 2004a; West et al., 2014).

Results from the RCT demonstrated superiority of CFF-CBT versus a dose-matched, enhanced TAU control in terms of treatment attendance and satisfaction, children's manic and depressive symptoms, and global functioning (West et al., 2014). Moderator analyses indicated that CFF-CBT was most impactful for parents with severe depression and low income, and families with high cohesion (Weinstein, Henry, Katz, Peters, & West, 2015). In addition, children with milder depression and greater self-confidence fared more poorly in TAU. However, mechanisms of change in CFF-CBT have not yet been examined.

1.4. Purpose of current study

As CFF-CBT targets family functioning, parenting skills and coping, and child coping impaired among youth with PBD, and based on research supporting the role of parent and family