Published in final edited form as:

J Clin Child Adolesc Psychol. 2013 ; 42(5): 734–747. doi:10.1080/15374416.2013.817312.

Future Directions for Research on Youth with Bipolar Spectrum Disorders

Mary A. Fristad and Guillermo Perez Algorta

The Ohio State University

Keywords

child; adolescent; bipolar disorder; assessment; treatment

When I (XXX) began my training in clinical child psychology in 1981, childhood depression was a highly controversial diagnosis as children did not have superegos, and therefore, could not become depressed. I had the good fortune to work with a childhood mood disorders research team starting in my second year of graduate school, so rather than learning these clinical conventions, I learned how to diagnose children instead. Thanks to several active research groups, considerable research was launched in that decade. However, in 1989, at a national conference, a prominent researcher cornered me to ask, “Now XXX, do you *really* think that kids can get depressed?” In sum, the 1980s were definitely a time of diagnostic evolution for childhood depression.

Continuing on the evolutionary trail, the decade of the 1990s was essentially the birth of childhood bipolar disorder. Again, as a fledgling clinical researcher, I was oblivious to the mindset that this diagnosis couldn’t exist, as we were enrolling children with bipolar disorder into treatment trials. However, research was very limited; I could fit all the articles on the topic into one file drawer. The decade culminated in 1999 with the publication of “The Bipolar Child” by D. and J. Papolos (1999). Subsequently, the pendulum was unleashed, and like any self-respecting pendulum, it swung from “there is no such diagnosis in children” to the “every ‘rage’ is a sign of bipolarity”. As a result, there has been tremendous confusion in the field. Fortunately, there has also been an exponential growth in research on the topic, as we outline later in this paper.

Below, we summarize what is currently known about the basic phenomenology of pediatric bipolar disorder (more correctly thought of as bipolar spectrum disorder, or BPSD), its clinical course, assessment and treatment, beginning with a summary of major studies that have shed light on the topic. Next, we present a tally and content review of current research being conducted as an indicator of future trends. Then, we describe what we believe are important future directions for research. Finally, we conclude with implications for contemporary clinicians and researchers.

What We Know Now

Influential Studies

Data are emerging from multiple large cross-sectional and longitudinal studies. Most influential are the “EDSP-Bavarian Catchment” study (Beesdo et al., 2009), the Course of Bipolar Youth “COBY” study (Birmaher et al., 2006), the “Stanley” study (Findling et al., 2005), the Longitudinal Assessment of Manic Symptoms “LAMS” study (Findling et al., 2010) the Prepubertal and Early Adolescent Bipolar Disorder “PEA-BD” study (Geller et al., 1998), the Oregon Adolescent Depression Project “OADP” (Lewinsohn, Klein, & Seeley, 1995), the “Boston” study (Wozniak et al., 2011) and the Assessing Bipolar Disorder: A Community-Academic Blend study “ABACAB” (Youngstrom et al., 2005). Table 1 provides an overview of these studies’ methodologies.

Definitions

Bipolar Spectrum Disorders (BPSD) are a collection of diagnoses that, in DSM-5, includes: Bipolar I (BP1: full mania, usually has full depression although this is not required), Bipolar II (BP2: hypomania plus full depression), Cyclothymic Disorder (CYC: subthreshold manic and depressive symptoms persisting over a one-year minimum), and Other Specified Bipolar and Related Disorder (for purposes of this article, referred to as BP-NOS) (American Psychiatric Association, 2013).

Prevalence

Estimated prevalence in adults is 1.0% for BP1 and 1.2% for BP2 (Merikangas et al., 2011; Pini et al., 2005; Weissman et al., 1996). Evidence from clinical and epidemiological studies suggests subthreshold presentations represent clinically significant syndromes (Angst et al., 2010). Prevalence of these milder presentations in adults ranges from 4% to 6% (Angst, Gamma, & Lewinsohn, 2002; Merikangas et al., 2007; Zimmermann et al., 2009).

Estimated prevalence in adolescence is 1.8%, based on a meta-analysis of 12 studies that included 16,222 youth aged 7 to 21 (Van Meter, Moreira, & Youngstrom, 2011). Slightly higher rates were reported in a recent community sample of 10,123 adolescents; Merikangas and colleagues (2012) reported an estimated lifetime prevalence of 2.5% for BP1 or BP2, with a two-fold increase in rates of mania from ages 13-14 to 17-18. Variability of these estimates is due at least in part to methodological differences in assessment and diagnostic criteria for mania and depression (Van Meter et al., 2011). Despite this variability, these estimates support findings from retrospective studies in adult community samples that indicate onset of BPSD often emerges prior to age 18 (Baldessarini et al., 2012; Perlis et al., 2004). As adolescent rates are currently similar to adult rates, this provides further evidence that rates are increasing with each passing generation since World War II, as one would expect adolescent rates to be lower than adult rates unless all cases onset prior to adulthood (Gershon, Hamovit, Guroff, & Nurnberger, 1987). Further indication of a rise in BPSD is suggested by a comparison of MMPI hypomania scale scores from the 1930s-40s to the 1990s-2000s, during which time scores increased by a standard deviation; by 2007 94% of college students scored above the original mean (Twenge et al., 2010).

Clinical Course

Although BPSDs are episodic in nature, they can present with or without inter-episode recovery (Kowatch, et al. 2009). Cardinal symptoms include elevated mood, grandiosity and decreased need for sleep, while the most common symptoms of BPSD are increased energy, distractibility, and pressured speech (Kowatch, Youngstrom, Danielyan, & Findling, 2005).

Comorbidity is the rule, not the exception. The high comorbidity rate highlights the need for methodologic rigor when diagnosing (Danner et al., 2009). Various disorders share many overlapping symptom presentations with BPSD, this may reflect some underlying processes shared by what are putatively distinct conditions (Youngstrom & Algorta, 2013).

In 2011, the World Health Organization listed BPSD as the fourth leading cause of disability among adolescents ages 15 to 19 years worldwide (Gore et al., 2011). This lends support to previous studies that reported youth with BPSD have a lower quality of life than those with other chronic medical conditions such as asthma and obesity, as well as other common mental disorders, including unipolar depression and behavioral disorders (Freeman et al., 2009). Youth with BPSD typically experience significant impairment in academic functioning as well as in social interactions (Geller et al., 2000). While in a mood episode, these difficulties are intensified (Goldstein et al., 2009). Additionally, youth with BPSD are more likely to engage in suicidal behavior (Goldstein, 2009). Notably, early presentation of BPSD is linked with a high rate of suicide attempts (Goldstein et al., 2012).

Assessment

Instruments—With the exception of astute observers such as Kraepelin (1921), bipolar disorder in children essentially was not considered a diagnostic possibility until recently. It is not surprising that BPSD in children was not well understood in earlier eras, first when psychodynamic theory reigned and projective testing was the common assessment method and later, when the combined influence of a behavioral backlash against psychodynamic thinking and advent of the world wars led to paper-and-pencil measures and behavioral/empirical approaches to assessment. These movements did not lead to consideration of the diagnosis, either. Not until structured interviews began to be used were children routinely queried in a systematic manner about mood symptoms. Initially, adult interviews were adapted and validated for use with children (Fristad, Weller, & Weller, 1992a); later, instruments were developed specifically for children (Rooney, Fristad, Weller, & Weller, 1999). In particular, the Children's Schedule for Affective Disorders & Schizophrenia (K-SADS) (Chambers et al., 1985), the Diagnostic Interview for Children and Adolescents-Revised (DICA-R) (Reich & Welner, 1988), the *Diagnostic Interview Schedule for Children* (DISC) (Costello, Edelbrock, & Kalas, 1982), and the *Interview Schedule for Children* (ISC) (Kovacs, 1985) have been used, and more recently, the *Children's Interview for Psychiatric Syndromes* (ChIPS) (Rooney et al., 1999). How these instruments have been used has varied by site and by study, yielding heterogeneous results that offer some difficulty in terms of integration (Galanter, Hundt, Goyal, Le, & Fisher, 2012).

In addition to structured and semi-structured interviews, symptom severity measures have been adapted or developed then validated. These include the Young Mania Rating Scale

(YMRS) (Fristad, Weller, & Weller, 1995; Fristad, Weller, & Weller, 1992b), the parent and self-report General Behavior Inventory (P-GBI, GBI), long and brief (PGBI-10M) versions (Danielson, Youngstrom, Findling, & Calabrese, 2003; Youngstrom, Findling, Danielson, & Calabrese, 2001; Youngstrom, Frazier, Demeter, Calabrese, & Findling, 2008; Youngstrom et al., 2004), the Child Bipolar Questionnaire (Papolos, Hennen, Cockerham, Thode, & Youngstrom, 2006), the Child Mania Rating Scales (CMRS) (Pavuluri, Henry, Devineni, Carbray, & Birmaher, 2006), the Mood Disorder Questionnaire for adolescents (MDQ-A) (Wagner et al., 2006) and subscales extracted from popular screening measures such as the Child Behavior Checklist (CBCL) (Biederman et al., 1995).

Controversies and conventions—Just as there are conservatives, liberals and moderates on any topic, these positions are held in regard to childhood-onset BPSD. A conservative (or “narrow” phenotype, according to Leibenluft and colleagues [2003]) requires episodicity. In addition, requiring elated mood and grandiosity as cardinal symptoms, an approach used in the PEA-BD study, prevents children with chronic irritability as the only “manic” mood state from being labeled bipolar (Geller, Zimmerman, Williams, Delbello, Bolhofner, et al., 2002; Geller, Zimmerman, Williams, Delbello, Frazier, et al., 2002).

The liberal position, or “broad phenotype” (Leibenluft et al. 2003) includes youth whose mood is predominantly irritable, lacking clear periods of elated mood or grandiosity (Nottelmann et al., 2001). This is consistent with the observation that adults with BD present primarily with irritable, not elated mood (Judd et al., 2002). The Boston group, headed by Biederman, has described irritable moods as a core feature of BPSD and argued that non-episodic presentations are common on the bipolar spectrum (Mick et al. 2005; Wozniak et al. 2005).

An intermediate position, aligned with DSM-5, acknowledges that irritable mood, if episodic, can be part of the bipolar spectrum, although grandiosity and/or elated mood are very frequently present. This position is consistent with the COBY, LAMS, Stanley, ABACAB, EDSP-Bavarian Catchment and OADP studies.

To more carefully differentiate broad and narrow phenotypes, Leibenluft and colleagues (2003) proposed a new category, “severe mood dysregulation” (SMD). SMD requires that children display increased reactivity to negative emotional stimuli in the form of severe rages, and chronic hyperarousal (insomnia, motor hyperactivity, distractibility, racing thoughts or flight of ideas, etc). SMD also specifies that the child exhibits abnormal mood between rages (sadness or anger) and that symptoms are chronic and cause impairment at least in two settings. Numerous studies have compared a cohort of youth with bipolar disorder to those with SMD (Leibenluft, 2011) and a recent review compares and contrasts SMD with BP-NOS (Towbin, Axelson, Leibenluft, & Birmaher, 2013). Differences have been observed in terms of affective response and cognitive flexibility (Dickstein et al., 2007; Guyer et al., 2007; Rich et al., 2010), functional imaging (Adleman et al., 2012; Adleman et al., 2011; Rich et al., 2011) and family history (Brotman et al., 2007).

In an attempt to decrease a perceived overdiagnosis of bipolar disorder, the DSM-5 working group developed a new diagnosis, disruptive mood dysregulation disorder (DMDD). This is a modified version of SMD, not requiring chronic hyperarousal symptoms and having fewer exclusionary criteria. Initially considered for inclusion as a disruptive behavior disorder, it was moved to the mood disorders group. Inclusion of DMDD in DSM-5 has been controversial; concerns include limited research to support the DMDD diagnosis, as available data refer mainly to SMD (Axelson et al., 2012). Its prevalence is highly dependent on how frequency, persistence, and duration criteria are applied (Copeland, Angold, Costello, & Egger, 2013). Test-retest reliability is low ($\kappa=0.25$) (Regier et al., 2013). Results from LAMS indicate DMDD: 1) symptoms are common in outpatients; 2) is not delimited from oppositional defiant disorder and conduct disorder; 3) has limited diagnostic stability; and 4) is not associated with current, future-onset or parental history of mood/anxiety disorders (Axelson, 2013). In summary, findings raise concerns about the diagnostic utility of DMDD in clinical populations (Axelson et al., 2012; Axelson, 2013).

Treatment

Pharmacologic guidelines—Pharmacologic trials have increased rapidly and have led to updated treatment algorithms, placing atypical antipsychotics ahead of mood stabilizers as the initial treatment of choice (Correll, Sheridan, & DelBello, 2010; Goldstein et al., 2012). Treatment response is promising; improvement in acute manic and mixed episodes in adolescents resembles outcomes observed in adults. Unfortunately, although atypical antipsychotics provide notable symptomatic relief, they also carry a high burden vis a vis their metabolic side effects (Goldstein, Sassi, & Diler, 2012). Despite significant amelioration of symptoms, psychopharmacologists agree that psychosocial interventions are essential to minimize the burden of psychotropics as well as to maximize recovery (McClellan, Kowatch, & Findling, 2007). (Colom, Vieta, & Scott, 2006).

Psychotherapy—In terms of psychosocial treatment, significant progress has been made over the past 10 years. A review in 2002 indicated no clinical trials existed (Fristad et al, 2002). Since then, numerous psychosocial interventions have been evaluated (MacPherson & Fristad, in press). Although no *well-established* treatments exist, family psychoeducation plus skill building (i.e., Multi-Family Psychoeducational Psychotherapy, Fristad et al, 2009; Family-Focused Treatment, Miklowitz et al, 2008) is considered *probably efficacious*; cognitive-behavioral therapy (CBT) is *possibly efficacious* (Pavuluri et al, 2004; West et al., 2009; Feeny, Danielson, Schwartz, Youngstrom, & Findling, 2006); dialectical behavior therapy (DBT: Goldstein et al, 2007) and interpersonal and social rhythm therapy (IPSRT: Hlastala et al, 2010) are considered *experimental*. RCTs of family psychoeducation plus skill building, CBT and DBT are underway and will add to the empirical basis for clinical decision making regarding psychosocial treatment.

We have some knowledge of predictors, mediators and moderators of treatment, although more investigation of these is needed. Teaching families about evidence-based treatments leads to improved quality of services received, which lead to improved outcomes (Mendenhall, Fristad, & Early, 2009). Family psychoeducation plus skill building appears to

be particularly effective for more severely impaired youth from highly troubled families (Miklowitz et al., 2009; MacPherson, Algorta, Mendenhall, Fields, & Fristad, in press).

What We Are Learning Now

Publication Trends and Topic Review

Procedures—To visualize the trajectory and focus of scientific publications about BPSD in youth, we first tallied papers published in PubMed under the heading “pediatric” or “child” or “adolescent” AND “bipolar disorder” or “mania” from the time of the first contemporary citation observed (November, 1952) until February, 2013. Second, we reviewed a more recent subset of these papers, all those listed in PubMed under the subject heading “pediatric” AND “bipolar disorder” from January 2005 through July 2012. We chose this strategy as we believed it best approximated what clinicians and consumers would be interested in—recent articles with relevant search terms. Papers were classified into one of ten categories (review, neuroscience, pharmacology, psychosocial treatment, phenomenology, assessment, risk factors, case examples, economical disease burden and a combination category, neuroscience and pharmacology). Each article was reviewed by two trained undergraduate raters; discrepancies were discussed with the second author (XXX) to arrive at a final consensus.

Results—From November, 1952 through February, 2013, 7140 papers were listed in PubMed using our search terms (see Figure 1). The most recent five year interval, 2006 – 2010, indicates the largest increase in number of publications (n=2060, 29% of the total). To date in the 2011-2013 interval, 834 articles have been published. A subset of 380 papers selected using the criteria described previously received a content review. Frequency of article type appears in Table 2. The review category was most prevalent (n=112, 30%) followed by neuroscience (n=86, 23%) and pharmacotherapy (n=52, 13%). Far fewer papers focused on economic burden, psychosocial aspects or psychotherapy.

Emerging Findings

A growing consensus based on clinical data suggests that BPSD can be a progressive disease. Neuroscience findings call for the importance of tracking progression of underlying processes from early manifestations of the disease onward. This step is considered necessary to clarify neurophysiology prior to the confounding effects of medication exposure and illness course (Schneider, DelBello, McNamara, Strakowski, & Adler, 2012). Several provocative hypotheses have been proposed: increased cortical volume might represent failed pruning; white matter abnormalities (i.e., connections among brain regions) may exist prior to illness onset. These alterations in neurodevelopment may lead to affective dysregulation and eventual onset of the first manic episode. These hypotheses require studies of narrowly defined groups, longitudinal studies across mood states and treatment response, and monitoring of early course progression compared to other conditions (Strakowski et al., 2012). LAMS, currently in its ninth year, is an example of this kind of study as it gathers clinical, neuroimaging and neurocognitive data (Findling et al., 2010).

However, there is not full agreement that BPSD is a chronic progressive disease. For example, Cicero and colleagues reported an abrupt decrease in past-year prevalence of BPSD observed during the third decade of life (Cicero, Epler, & Sher, 2009). These striking results led the researchers to postulate the possibility of two earlier variants of BPSD; one relatively severe with poor prognosis and another developmentally limited form with (relatively) good prognosis. Clearly, more prospectively gathered longitudinal data are needed to advance our conceptualization of BPSD. In addition, sample sources need to be delineated to account for potential selection biases (Berkson, 1946). Clinical and epidemiological studies are both valuable, but will explicate different aspects of the illness.

What We May Learn—Future Directions

The Impact of Research Domain Criteria (RDoC)

Allocation of research resources is determined by guidelines offered by funding federal and private agencies. We have witnessed a recent shift in these guidelines after publication of the *National Institute of Mental Health Strategic Plan* (National Institute of Mental Health [NIMH], 2012) (<http://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml>), the goal of which is to develop a new approach to define constructs for integrative research purposes. NIMH is suggesting new ways to classify mental disorders based on dimensions of observable behavior and neurobiological measures (Morris & Cuthbert, 2012).

The Research Domain Criteria (RDoC) project, the roots of which can be traced to Hyman and Fenton's (2003) paper decrying the paucity of successful treatment development in our broader field, favors an integrative approach to research. The RDoC framework, summarized in Table 3, includes a set of "superordinate" research domains comprised of multiple, more specific constructs and subconstructs. Methods to examine these domains, constructs and subconstructs include: genes, molecules, cells, circuits, physiology, behavior and self-reports. For example, "circuits" implies measures that can index the activity of neural circuits, traced by previous validated methodologies such as functional neuroimaging. "Self-reports" refers to the use of questionnaires or scales that cover aspects of the dimension under study. If studying a domain relevant for BPSD, for example, we could select "Positive Valence Systems", and focus on the construct "approach motivation" and subconstruct "reward valuation". Examples of research underway utilizing this framework include studying the role of dopamine and serotonin at the level of molecules and evaluating corticolimbic and ventral tegmental areas at the level of circuits. The BAS reward-sensitive subscale is an example of a relevant self-report measure. For a detailed description of each domain, please refer to http://www.nimh.nih.gov/research-funding/rdoc/rdoc-constructs.shtml#active_threat. This framework is acknowledged to be a starting point that reflects the current state of knowledge as well as a desired direction of future focus (Sanislow et al., 2010).

It is hoped that RDoC will result in a better understanding of underlying dysfunctions in various conditions, promoting the development of more effective treatments (Craske, 2012). NIMH's intention is that by altering the focus from the current DSM categorical diagnostic system to new dimensional approaches based on (not yet understood) biological factors,

scientific breakthroughs will occur, leading to improved treatment. For example, neuroimaging data from the LAMS study indicates that response to a self-report measure (the PGI-10M) irrespective of diagnosis (bipolar or not bipolar) is associated with reward sensitivity and attention to reward on various neuroimaging tasks (Bebko et al., in press). Discovering objective biomarkers that reflect underlying pathophysiologic processes could likely lead to improved pharmacology; it is possible that these discoveries would also contribute to more tailored psychosocial interventions. Ultimately, integration of information from various RDoC domains in addition to environmental risk and resiliency factors, may lead to increased understanding of treatment predictors, mediators and moderators. This, in turn, should lead to more personalized interventions as well as new avenues to monitor treatment response. The ultimate goal is prevention, recovery and/or cure.

The Role of Technology

As stated clearly by Craske (2012), implementing an RDoC model into clinical practice will be challenging. It is possible that (relatively) novel technological devices (e.g., smartphones) utilizing strategies such as experience sampling method or ecological momentary assessment (Csikszentmihalyi & Larson, 1992; Stone & Shiffman, 1994; Trull & Ebner-Priemer, 2013) will play a role in clinical and research endeavors. Physiologic and self-report measures could be measured in real time. This strategy brings with it multiple new challenges. Research to develop reliable, valid real-time measurement is needed, followed by therapeutic trials to determine how real-time coaching or other interventions could be used to provide highly personalized and timely intervention to individuals with BPSD.

As an example, daily monitoring of mood changes could permit identification of individual disease patterns, providing new avenues to early detection of full episodes, as well as dynamic treatment adjustments, taking into account each temporal signature pattern. This has the potential to lead to development of precise prognostic models and personalized, timely treatment, including prevention of suicide. Several germinal examples of teletherapy for different disorders in adults (Nelson, Bui, & Velasquez, 2011) hint at novel ways in which personalized care might be delivered in the future. These new treatment strategies have the potential to reach populations without easy access to services and reduce costs associated with treatment provision (Kazdin & Blase, 2011). Treatment might include modules on: adherence to pharmacological and psychosocial interventions; sustaining a regular sleep pattern; identifying mood features; developing cognitive restructuring strategies; enhancing relaxation techniques; and could include real-time reward systems and provision of personalized feedback. It may also be possible, via technology, to improve communication strategies with family members and other supports in a child's life.

Some work has already been done in this area, mainly with adult samples, with various methodological strategies and technological devices capturing the dynamic nature of BPSD, including temporal pattern changes that document variability of mood and the episodic, cyclic nature of the illness (Bauer et al., 2004; Bopp et al., 2010; Depp et al., 2010; Fulford, Johnson, Llabre, & Carver, 2010; Havermans, Nicolson, & Devries, 2007; Havermans, Nicolson, Berkhof, & deVries, 2010, 2011; Husky et al., 2010; Knowles et al., 2007;

Miklowitz et al., 2012; Myin-Germeys et al., 2003). Only one feasibility study has evaluated pediatric affective disorders (Axelson et al., 2003). In this study, 17 of 21 participants completed an 8-week protocol, in which information was collected through short telephone calls (3.4 minutes on average). Participants were reported to enjoy the experience.

Ethical considerations, particularly with younger clientele, will be important to address. Learning how to condense, analyze and interpret the potentially vast amounts of data collected by these devices will be critical. Fortunately, several advances in terms of data analysis should enhance this development (Bolger & Laurenceau, 2013; Mehl & Conner, 2012; Walls & Schafer, 2006), but currently, little is known about the clinical utility of such efforts.

The Gut as the Second Brain

Long before the advent of sophisticated pharmacological treatment algorithms, our current first line treatments, the importance of nutrition in the care of patients was noted.

“The *nutrition* of the patients demands special attention. An abundance of nutritious and easily digested food should be given the patients at regular intervals... The food should be carefully selected and easily digestible” (Diefendorf & Kraepelin, 1907).

More recently, nutrients in the treatment of BPSD in youth have been empirically investigated. Early results suggest utilization of complementary and alternative treatments (CATs) may decrease the number and/or dosage of psychotropic medications needed to achieve treatment response with minimal side-effects (Frazier, Fristad, & Arnold, 2009; Frazier, Fristad, & Arnold, 2012; Frazier et al., 2013; Scheffer, 2008). Intriguing work on the role of Vitamin D in mood impairment suggests that Vitamin D deficiency is associated both with severity of mood symptoms and psychosis (Gracious, Finucane, Freidman-Campbell, Messing, & Parkhurst, 2012). Many more questions than answers exist at present, including the most beneficial dose and ratio of EPA:DHA in the case of omega3 fatty acids, the ideal range of Vitamin D for mood stabilization, and determining which are the critical ingredients in a multi-nutrient intervention; however, pursuit of these questions may lead to treatments with a favorable risk:benefit ratio.

Psychosocial Interventions

We know much more now than we did in 2002, when a review indicated no evidence-based treatments for BPSD in youth. As more RCTs are completed, predictor, moderator, mediator, and dismantling analyses will be important to conduct. Such findings should indicate variables associated with treatment response, for whom interventions are most impactful, mechanisms of change, and essential treatment components (MacPherson & Fristad, in press). In addition, treatments that focus on reducing suicidal behavior, substance abuse, and risky sexual behavior are critical. Adding psychoeducational interventions to pharmacotherapy has been demonstrated to produce greater symptom stabilization, reduction in relapse rates, longer time to relapse, and improved quality of life in adults (Stafford & Colom, 2013). Studies that investigate an acute-phase treatment followed by

ongoing booster sessions are needed to determine if similar longer-term outcomes occur in youth.

As youth with BPSD spend a significant portion of their life in school settings, and as BPSD can affect school functioning in a myriad of ways, developing evidence-based interventions for use in school settings will be important. Impairment from manic and depressive symptoms, as well as common comorbid conditions can lead to undesirable scholastic and social consequences. Adding to these difficulties are side effects caused by medications prescribed for BPSD and lack of familiarity school personnel have with the diagnosis (Fields & Fristad, 2009). Existing psychosocial interventions already attend in some detail to school-based issues. We need evidence-based guidelines on how to best support learning, both social and academic, as well as vocational training, so that youth with BPSD can develop into successful adults, maintain meaningful relationships and obtain and retain gainful employment. Finally, methods to best disseminate effective management strategies in school settings are needed (George, Taylor, Schmidt, & Weist, 2013).

DMDD has been added to the Mood Disorders section of DSM-5 although cardinal symptoms are a combination of mood (irritable) and behavior (extreme temper tantrums). Studies are needed to determine what interventions will best treat DMDD; we suspect a combination of active ingredients from evidence-based treatment models for oppositional behavior as well as for mood disorders (outlined at www.effectivechildtherapy.com) may provide the most robust results. In particular, we anticipate emotion-regulation strategies (cf., Southam-Gerow, 2013) will be critical to ameliorate symptoms as well as their reverberating effects on the family system.

Combination Treatments

Combination treatments have been demonstrated to be advantageous in treating other disorders, including anxiety (Walkup et al., 2008), adolescent depression (March et al., 2004; March et al., 2007), pervasive developmental disorders (Aman et al., 2009), and ADHD (MTA Cooperative Group, 1999a, 1999b, 2004a, 2004b). Given the relatively rapid, but incomplete symptomatic relief of pharmacologic agents, coupled with their adverse effects, the need for combination trials of medications with psychosocial interventions and/or other CATs is apparent. For example, it has been demonstrated with ADHD that when evidence-based behavioral interventions are employed, lower doses of psychotropics are needed to achieve the same outcomes with fewer untoward side effects (Pelham, Fabiano, & Massetti, 2005). Exploration of combination treatments for BPSD is warranted. One such study underway is the Omega3 and Therapy Study (OATS: R34 MH0900148-03A1), in which the impact of omega 3 fatty acids versus placebo and individual-family psychoeducational psychotherapy versus active monitoring, are being compared in a 12-week clinical trial.

Additional Questions

Treatment guidelines are limited to BP1 and BP2; evidence-based guidelines are not available for CYC and BP-NOS. As Youngstrom et al (2013) suggest, treatments with an ideal risk:benefit ratio may differ, based on severity of symptom presentation. Much more

work is needed to learn the “doses” of psychotherapy, CATs and/or psychotropic medication that are needed to maximize functional capacity at varying levels of symptom severity.

Drug and alcohol abuse are frequent sequelae of BPSD; substance abuse complicates both diagnosis and treatment. Despite being a very significant problem, it has received limited attention. To date, only clinical vignettes are available to guide thinking (Miklowitz, 2012). Methods to enhance prevention of substance use and abuse in this highly vulnerable population are needed.

In addition, much more work is needed to develop effective, evidence-based guidelines for bipolar depression, maintenance treatment, and the simultaneous amelioration of comorbid conditions (Liu et al., 2011; Thomas, Stansifer, & Findling, 2011). The earlier the age of onset, the further the child falls off the developmental trajectory. Recovery models are needed to improve long-term prognosis.

Our categorical and dimensional labels for BPSD may change over time. One immediate change, ushered in with DSM-5, is the inclusion of DMDD in the mood disorders category. Following the established Robins and Guze criteria (1970) expanded upon for children by Cantwell (1996), multiple steps are needed to demonstrate diagnostic validity: clinical descriptions, laboratory studies, exclusion of other disorders, follow-up studies, family environmental and genetic factors, psychosocial elements, demographic features and response to therapeutic intervention. These features warrant examination in regard to DMDD to determine if the diagnosis will pass this level of scrutiny and remain in DSM-5.1.

The availability and cost of various imaging and genetic tests is steadily decreasing. As advances are made in our understanding of the pathophysiology of disease, more precise treatment targets may be developed and/or existing treatments may be used with greater precision. In particular, risk profiling may improve; currently, our best combination of predictors accounts for less than half of the variance for those who present with BPSD (Fristad et al., 2012). Similarly, new technologies may provide more cost-efficient and effective means of real-time assessment and treatment delivery.

Finally, improvement in dissemination of evidence-based assessment and treatment (EBAT) practices is needed. In a recent survey of providers and consumers, providers indicated the need for more training in EBAT for BPSD, while consumers reported overall satisfaction with non-specific aspects of care but frustration with the infrequent use of EBAT by providers (Chung, Vesco, Resko, Schiman, & Fristad, 2012).

Implications for Clinicians and Researchers

We know much more about pediatric BPSD than we did 25 years ago. There is growing consensus around its portrayal as a spectrum of disorders, its characteristics when onset occurs in childhood or adolescence, and its multi-modal treatment. We know enough to imperfectly ascertain risk, diagnose, treat, and support families through very challenging situations.

Subsequent to a thorough diagnosis that clarifies the nature of BPSD and its comorbid conditions, biological interventions are the agreed upon first-line of treatment. However,

general consensus is that psychosocial interventions are essential to promote overall functional capacity, as opposed to the more narrow goal of symptom reduction. While nuanced differences exist between various psychotherapeutic approaches, their commonalities are more striking. Until dismantling studies are conducted to provide more precise guidance, clinicians are recommended to utilize the common, apparently active ingredients of these treatments in clinical practice. These include: family involvement; psychoeducation about etiology, symptoms, course, medications, risk and protective factors, and effective treatment of BPSDs; skill building (especially communication, problem-solving, CBT, sleep hygiene, activity scheduling, zeitgebers and emotion regulation skills); and relapse prevention drills. However, much more needs to be learned to improve treatment response and ultimately, prevent and/or cure BPSD in youth.

Acknowledgments

This paper was supported by three National Institute of Mental Health (NIMH) funded studies: R01 MH073801 Longitudinal Assessment of Manic Symptoms (LAMS); R34MH085875; R34 MH090148. The findings and conclusions presented in this paper are those of the authors alone and do not necessarily reflect the opinions of NIMH. We especially thank Jennifer Lehmann B.A. and Manisha Patel B.A. for their contributions to the review presented in this manuscript.

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Figure 1.
Number of publications per epoch from 1952 to 2010.
Note: Citations are per epoch

Table 1
Major Longitudinal Studies of Bipolar Spectrum Disorder in Youth

Main citation and name of study	Type of study	Sample size [*]	Age range covered	Diagnostic Interview and Algorithm used
Beesdo, et al., 2009, "EDSP - Bavarian Catchment"	Longitudinal, community	3,021	14 - 34	DIA-X/M-CIDI DSM-IV
Birmaher, et al., 2006, "COBY"	Longitudinal, clinical	446 [*]	7 - 17y11m	K-SADS-PL DSM-IV
Findling, et al., 2005, "Stanley"	Longitudinal, clinical	400	4 - 20	K-SADS-E or K-SADS-PL ^a DSM-IV unmodified
Findling, et al., 2010, "LAMS"	Longitudinal, clinical	707	6y0m - 17y11m	K-SADS-PL-W DSM-IV unmodified
Geller, et al., 1998, "PEA-BD"	Longitudinal, clinical	120	7 - 18	WASH-U KSADS DSM-IV
Lewinsohn, et al., 1995, "OADP"	Longitudinal, community	1,709	14 - 34	K-SADS-E and K-SADS-P DSM-III-R
Wozniak, et al., 2011, "Boston"	Longitudinal, clinical	78	6 - 20	KSADS-E or SCID DSM-IV
Youngstrom, et al., 2005, "ABACAB"	Longitudinal, clinical Cross-sectional	262 614	5 - 18	K-SADS-PL-W ^a DSM-IV unmodified

"EDSP": The Early Developmental Stages of Psychopathology study

"COBY": Course and Outcome for Adolescent with Bipolar Illness

"LAMS": Longitudinal Assessment of Manic Symptom Study

"PEA-BD": Prepubertal children and early adolescents with bipolar disorders

"OADP": Oregon Adolescent Depression Project

"ABACAB": Assessing Bipolar Disorder: A Community-Academic Blend study

DIA-X/M-CIDI: Munich-Composite International Diagnostic Interview

SCID: Structured Clinical Interview for DSM-IV

K-SADS: Schedule for Affective Disorders and Schizophrenia for School Age Children

K-SAD-E: Epidemiological version

K-SADS-P: Present Episode

K-SADS-PL: Present and Lifetime Version

K-SADS-PL-W: as above, includes additional depression and manic symptom items from the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS)

^{*} Note: Sample size has been updated taking into account information provided in posterior publications.

^a Diagnostic information was cross-sectional

Table 2
Article Coding Categories, Definitions and Frequencies for 7.5 Years (N= 380) of Articles
Focused on Pediatric Bipolar Disorder

Category	Definition	Frequency (%)
Review	Reviews empirical work of others	30
Neuroscience	Focuses on brain structure and/or function	23
Pharmacology	Investigates impact of medications	13
Phenomenology	Examines demographic and clinical variables affecting incidence or clinical features	11
Assessment	Explains current or new measures to assess or diagnose	8
Risk Factors	Assesses high-risk offspring, other factors that could increase rate of diagnosis	6
Case Examples	Provides detailed description of the phenomenology, assessment, and/or treatment of a specific individual, family or group	3
Neuroscience & Pharmacology	Focuses on interaction of medication and neuroscience	3
Psychosocial Aspects	Focuses on relationships with peers and family, quality of life	1
Economical Disease Burden	Studies related with the economic cost associated to BPSD	1
Psychological Treatment	Investigates impact of psychological treatment	1

Table 3
National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) Outline

	Units of Analysis							
Domains/Constructs	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Positive Valence System^a								
Approach motivation								
Reward valuation								
Effort valuation / Willingness to work								
Expectancy / Reward								
Prediction error								
Action selection / Preference-based decision making								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning Habit								
Cognitive Systems								
Systems for Social Processes								
Arousal/Regulatory Systems								

^aExample of subconstructs for this construct provided.