BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

The International Society for Bipolar Disorders Task Force Report on Pediatric Bipolar Disorder: Knowledge to Date and Directions for Future Research

Journal:	*Bipolar Disorders*
Manuscript ID	BDI-17-R-4240.R1
Wiley - Manuscript type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Goldstein, Benjamin; Department of Psychiatry, Birmaher, Boris; Professor of Child Psychiatry, Carlson, Gabrielle; Professor of Psychiatry and Pediatrics DelBello, Melissa; Vice-Chair for Clinical Research, Department of Psychiatry, Findling, Robert; Johns Hopkins University, Department of Psychiatry Fristad, Mary; Professor, Psychiatry and Psychologyand Human Nutrition, Kowatch, Robert; Ohio State, Miklowitz, David; Professor of Psychiatry, Nery, Fabiano; University of Cincinnati College of Medicine, Psychiatry and Behavioral Neuroscience Perez-Algorta, Guillermo Van Meter, Anna; Yeshiva University, Ferkauf Graduate School Zeni, Cristian; University of Texas Health Science Center at Houston, Department of Psychiatry and Behavioral Sciences Correll, Christoph; The Zucker Hillside Hospital, Division of Psychiatry Research Kim, Hyo-Won Wozniak, Janet; Director, Pediatric Bipolar Disorder Research Program Chang, Kiki; Associate Professor, Stanford School of Medicine Hillegers, Manon; UMC Utrecht, Youngstrom, Eric; Professor of Psychology and Psychiatry
Keywords:	bipolar disorder, child, adolescent, pediatric, youth
Abstract:	Objectives: Over the past two decades there has been tremendous growth in research regarding bipolar disorder (BD) among children and adolescents (i.e., pediatric BD; PBD). The primary purpose of this article is to distill the extant literature, dispel myths or exaggerated assertions in the field, and disseminate clinically relevant findings. Methods: An international group of experts completed a selective review of the literature, emphasizing areas of consensus, identifying limitations and gaps in the literature, and highlighting future directions to mitigate these gaps. Results: Substantial, and increasingly international, research has accumulated regarding the phenomenology, differential diagnosis, course, treatment, and neurobiology of PBD. Prior division around the role of

	irritability and of screening tools in diagnosis has largely abated. Gold-standard pharmacological trials inform treatment of manic/mixed episodes, whereas fewer data address bipolar depression and maintenance/continuation treatment. Adjunctive psychosocial treatment provides a forum for psychoeducation and targets primarily depressive symptoms. Numerous neurocognitive and neuroimaging studies, and increasing peripheral biomarker studies, largely converge with prior findings from adults with BD. Conclusions: As data have accumulated and controversy has dissipated, the field has moved past existential questions about PBD toward defining and pursuing pressing clinical and scientific priorities that remain. The overall body of evidence supports the position that perceptions about marked international (U.S. versus elsewhere) and developmental (pediatric vs. adult) differences have been overstated, although additional research on these topics is warranted. Traction toward improved outcomes will be supported by continued emphasis on pathophysiology and novel therapeutics.

The International Society for Bipolar Disorders Task Force Report on Pediatric Bipolar Disorder: Knowledge to Date and Directions for Future Research

Benjamin I. Goldstein (Chair)[a,b]; Boris Birmaher[c]; Gabrielle A. Carlson[d]; Melissa P. DelBello[e]; Robert L. Findling[f]; Mary Fristad[g]; Robert A. Kowatch[g]; David J. Miklowitz[h]; Fabiano G. Nery[e]; Guillermo Perez-Algorta[i]; Anna Van Meter[j]; Cristian P. Zeni[k]; Christoph Correll[l]; Hyo-Won Kim[m], Janet Wozniak[n]; Kiki D. Chang[o]; Manon Hillegers[p]; Eric A. Youngstrom (Co-Chair)[q]

[a]Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada.

[b]Departments of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada.

[c]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

[d]Department of Psychiatry, Stony Brook University, Stony Brook, New York, USA

[e]Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati, Cincinnati, Ohio, USA.

[f]Department of Psychiatry & Behavioral Sciences, The Johns Hopkins University, Baltimore, Maryland, USA.

[g]Ohio State University Wexner Medical Center/Nationwide Children's Hospital, Columbus, Ohio, USA.

[h]Department of Psychiatry, UCLA, Los Angeles, California, USA.

[i]Division of Health Research, Lancaster University, Lancaster, England.

[j]Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, New York, USA.

[k]Department of Psychiatry, University of Texas, Houston, Texas, USA.

[l]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; and Hofstra Northwell School of Medicine, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA.

[m] Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea.

[n]Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

[o]Department of Psychiatry, Stanford University, Palo Alto, CA.

[p]Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center-Sophia, Rotterdam,The Netherlands

[q]Department of Psychology and Neuroscience, University of North Carolina, Chapel Hill, North Carolina.

Corresponding Author: Benjamin I. Goldstein

Sunnybrook Health Sciences Centre
2075 Bayview Avenue, FG-53
Toronto, ON M4N 3M5
Phone: 416-480-5328
Fax: 416-480-6818
Email: Benjamin.goldstein@sunnybrook.ca

Text: 7827 (not including references, figures, tables)

Disclosures:
Dr Birmaher receives funds for research by the National Institute of Mental Health. He receives royalties for publications from: Random House, Inc., Lippincott Williams & Wilkins, APA Press, and UpToDate.
Dr. Carlson receives funds for research from the NIMH and Patient Centered Outcomes Research Institute (PCORI)
Dr. Chang is an unpaid consultant for GSK, Lilly, and BMS. He is on the DSMB for Sunovion. In the past three years he has received research support from GSK and Merck, and has been a consultant for Actavis and Janssen.
Dr. DelBello received research support from NIMH, NIDDK, and PCORI, as well as Otsuka, Lundbeck, Sunovion, Pfizer, Johnson and Johnson, Supernus, Amarex, Shire; and has Consulting/Advisory Board/Honoraria from Pfizer, Lundbeck, Sunovion, Supernus, Takeda, Johnson and Johnson, Neuronetics, Akili.
Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Actavis, Akili, Alcobra, American Academy of Child & Adolescent Psychiatry, American Psychiatric Press, Bracket, CogCubed, Cognition Group, Coronado Biosciences, Elsevier, Epharma Solutions, Forest, Genentech, GlaxoSmithKline, Guilford Press, Ironshore, Johns Hopkins University Press, KemPharm, Lundbeck, Medgenics, Merck, NIH, Neurim, Novartis, Otsuka, PCORI, Pfizer, Physicians Postgraduate Press, Purdue, Rhodes

Pharmaceuticals, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, Takeda, Teva, Tris, Validus, and WebMD.
Dr. Fristad receives research funds from Janssen, publication royalties from Guilford Press, American Psychiatric Press and Child & Family Psychological Services, and honoraria from Physician's Post-Graduate Press.
Dr. Goldstein has nothing to disclose.
Dr. Hillegers has nothing to disclose.
Dr. Kim has nothing to disclose.
Dr. Kowatch is a consultant on data-safety monitoring boards for Forest and Pfizer; he is faculty for the REACH Institute.
Dr. Miklowitz receives funds for research from the NIMH and royalties from Guilford Press and John Wiley & Sons.
Dr. Nery held a position of Associate Medical Advisor in Eli Lilly & Co from 2012 to 2013. His spouse is an employee of Eli Lilly & Company. He received travel support from Janssen Pharmaceutical Co in 2016.
Dr. Perez Algorta has no disclosures/conflicts of interest.
Dr. Van Meter has no disclosures/conflicts of interest.
Dr. Wozniak has nothing to disclose personally; her spouse has received speaker honoraria from Otsuka, royalties from UptoDate, consultation fees from Advance Medical, FlexPharma, Merck; and research support from UCB Pharma, NeuroMetrix, Luitpold
Dr. Youngstrom has consulted with Pearson, Otsuka, Lundbeck, Joe Startup Technologies, and Western Psychological Services about psychological assessment, and receives funding from NIMH.

Abstract: 243 words

Objectives: Over the past two decades there has been tremendous growth in research regarding bipolar disorder (BD) among children and adolescents (i.e., pediatric BD; PBD). The primary purpose of this article is to distill the extant literature, dispel myths or exaggerated assertions in the field, and disseminate clinically relevant findings.

Methods: An international group of experts completed a selective review of the literature, emphasizing areas of consensus, identifying limitations and gaps in the literature, and highlighting future directions to mitigate these gaps.

Results: Substantial, and increasingly international, research has accumulated regarding the phenomenology, differential diagnosis, course, treatment, and neurobiology of PBD. Prior division around the role of irritability and of screening tools in diagnosis has largely abated. Gold-standard pharmacological trials inform treatment of manic/mixed episodes, whereas fewer data address bipolar depression and maintenance/continuation treatment. Adjunctive psychosocial treatment provides a forum for psychoeducation and targets primarily depressive symptoms. Numerous neurocognitive and neuroimaging studies, and increasing peripheral biomarker studies, largely converge with prior findings from adults with BD.

Conclusions: As data have accumulated and controversy has dissipated, the field has moved past existential questions about PBD toward defining and pursuing pressing clinical and scientific priorities that remain. The overall body of evidence supports the position that perceptions about marked international (U.S. versus elsewhere) and developmental (pediatric vs. adult) differences have been overstated, although additional research on these topics is warranted. Traction toward improved outcomes will be supported by continued emphasis on

pathophysiology and novel therapeutics.

Keywords: bipolar disorder, child, adolescent, pediatric, youth

1. Introduction

Over the past two decades there has been tremendous growth in the scientific literature regarding bipolar disorder (BD) among children and adolescents (i.e., pediatric BD; PBD) (Figure 1). The literature now contains numerous gold-standard clinical trials of pharmacological agents for mania, an increasing evidence base for adjunctive psychosocial treatments, several large-scale prospective clinical cohort studies, representative epidemiologic studies (particularly focused on adolescents) with international representation, numerous neurocognitive and neuroimaging studies, and an accelerating number of biomarker studies. Despite the volume, quality, and international spectrum of available literature, and regardless of the general consensus about some of the field's previously most divisive and controversial topics, there remains a perspective in the popular press, other branches of medicine, and even within mental health that the field of PBD lacks evidence and is replete with controversy. Therefore, the primary purpose of this article is to *distill* the extant literature, *dispel* myths or exaggerated assertions in the field, and *disseminate* clinically relevant findings. In this paper, an international group of experts completed a selective review of the extant literature (including PubMed and Web of Science/PsycINFO searches, querying other databases or conference proceedings and unpublished reports on an ad hoc basis), emphasizing areas of established findings and consensus, identifying limitations and gaps in the literature, and highlighting future directions to mitigate these gaps.

2. Epidemiology

Established findings and consensus

In community samples around the world, it is now well established that bipolar spectrum disorders—an umbrella that covers bipolar I, bipolar II, cyclothymic disorder, and bipolar Not Otherwise Specified (NOS) or Other Specified Bipolar and Related Disorders (OS-BRD)—occur in youths. The update of a published meta-analysis of epidemiological studies (1) using an identical search strategy identified six new studies satisfying inclusion criteria. The update includes 17 studies (7 from the USA) with 31,443 youth age 7-21 years, 576 of whom met criteria for bipolar spectrum disorders.(2-17) The updated weighted average prevalence rate of bipolar spectrum disorders is 2.06% (95% CI 1.44-2.95%).

There was substantial heterogeneity across studies, but it was not explained by year of data collection, lifetime prevalence (versus other time periods), or sex. Studies that included more adolescents had significantly higher prevalence estimates. Definitional differences of BD explained the largest portion of variance between studies. As expected, broader definitions (i.e., including NOS or cyclothymic disorder[CycD]) had the highest rates while narrow definitions (i.e., BD-I and II only) had lower rates, but even this was not a complete explanation. Weighted average prevalence of BD-I was 0.49% (95% CI 0.22-1.09%), with four of twelve studies reporting no BD-I cases. Although there is no epidemiological study on PBD in Asia, several studies from clinical samples reported that PBD is also prevalent in Asia.(18-20)

Community rates are not higher in the United States, nor do rates appear to be increasing over time. In contrast, billing and services data show a marked increase in rates of diagnoses in the USA over a 20-year period.(21, 22) Differences in training, conceptualization of cases and insurance demands appear more of a factor(23) than underlying differences in prevalence.

In summary, PBD prevalence rates appear relatively stable across studies. PBD is more common than autism or schizophrenia and much less common than depression or attention deficit hyperactivity disorder (ADHD) in the community, with higher rates after puberty more well established.(24)

Limitations, gaps, and future directions

New epidemiological studies need to systematically assess hypomania and mania and differentiate them from other non-mood psychopathology. Even the newest epidemiological data were collected at least ten years ago (range 1986-2005), and fewer than 1% of indexed papers on pediatric epidemiology include data about BD.(25) Documenting age of onset of the first mood episode of each type will be vital, with more studies including prepubertal children to clarify onset and course. If depression manifests first, it may not be clear that it is following a bipolar course until later. Onset age may be bimodal(26, 27) and American youth may be at higher risk for very early onset.(28) Existing literature confounds age and informant effects: studies with older participants are less likely to include interviews of parents. Studies relying only on retrospective self-report are likely to underestimate hypomania or mania, as people forget or minimize the events, whereas depression may be more salient. Using more consistent criteria across studies will reduce the largest source of variance identified in extant meta-analyses.

3. International findings

Established findings and consensus:

Prior studies in adults suggested that although BD occurs worldwide, there could be international differences in the clinical characteristics of BD, including age of onset, comorbidity, early adversity, and familiality.(29, 30) Although international differences in BD are less well-studied in youth as compared to adults, there now are PBD data from multiple countries including Australia/New Zealand, Brazil, China, France, India, Italy, South Korea, Spain, the Netherlands, Turkey, and the UK.(31) In addition to the epidemiological studies reviewed above, international BD data now include phenomenological,(19, 32-34) comorbidity,(19, 35) longitudinal,(36, 37) treatment,(38, 39) neuroimaging and biomarker,(40-42) and high risk studies.(43, 44) Numerous commentaries discuss purported international differences in the prevalence of PBD, which may be attributable either to including more subtypes,(25) differences in the interview method(45) and training,(23, 46) the type of sample studied (predominantly manic, depressive, treatment-seeking or registry), or a combination of these.(47)

Some findings converge with US data. For example, Brazilian families with PBD also show lower positive regard and higher negative expressed emotion (EE) compared to control families.(48) There are, however, examples of non-replication. In contrast to US data, a recent Brazilian imaging study did not find white matter microstructure differences between PBD youth, healthy bipolar offspring and healthy controls,(49) and parent report of youth mood symptoms showed much lower discriminative validity than parent report in other countries.(50) However, it is unclear whether this a true international difference or a difference owing to methodologic factors.

A recent study directly compared Dutch and US samples of offspring of parents with BD.(51) Both projects used the Achenbach Child Behavior Checklist (CBCL)(52) as well as similar semi-structured interviews (e.g., Kiddie Schedule for Affective Disorders and Schizophrenia)(53). After controlling for age, rates of DSM-IV BD-I (2.2% US, 1.5% Dutch) and BD-II (2% and 1%) were similar. In contrast, other disorders were significantly more common in the US sample, including depressive disorders (13% versus 4% in the Dutch sample), anxiety disorders (31% versus 9%), ADHD (22% versus 8%), and disruptive behavior disorder (19% versus 6%). CBCL Externalizing scores were higher in the US sample (15.0 +9.7 vs 10.8+7.6, p=0.03). However, Internalizing scores did not differ between samples (raw *M*~15), despite higher rates of anxiety and depressive disorders in the US sample. In the US, fewer parents had BD-I, affected parents were younger at their own illness onset, parental substance abuse rates were higher, and rates of parental employment and youth living with both biological parents were lower. These stressors may have contributed to the greater rates of problems in the US sample. The differences also illustrate the importance of the psychopathology of the parent bipolar sample to understanding rates of offspring psychopathology. The internalizing findings also suggest that there could be differences in clinical interpretation of similar levels of pathology, even using semi-structured approaches.

Limitations, gaps, and future directions:

Future work needs to determine whether there are meaningful international differences in the prevalence, phenomenology, course, treatment, and biology of PBD. Translating scales into multiple languages and pursuing cross-cultural validation is accelerating progress by using

consistent definitions(51), revealing considerable continuity in phenomenology.(54) Combining data sets internationally would help calibrate definitions and examine common risk factors.

4. Clinical Characteristics, Differential Diagnoses, and Course

Established findings and consensus

Clinical Characteristics

Interest in BD phenotypes spans decades. Over 25 years ago, the issue of severe chronic irritability as part of the bipolar spectrum polarized the field; this issue is now largely resolved.(47, 55, 56) With regard to symptom presentations, one position held that elation and/or grandiosity were required for a diagnosis of BD in youth.(57) There now is substantial consensus that chronic irritability, regardless of explosiveness or severity, is not sufficient for a diagnosis of BD, in contrast with formulations that focused on rages or severe aggression.(58) However, irritability is commonly present in youth with BD. Counting irritability as part of the diagnostic criteria for a manic or hypomanic episode requires either that the irritability begins or significantly increases in intensity *in conjunction with* the presence of accompanying manic (DSM Criterion B) symptoms. Thus, a youth with BPD *may* have chronic irritability, but the diagnosis would not be made based on that mood state.(59-62) Although severe irritability and emotional dysregulation are not proxies for BD, they are also not mutually exclusive of episodic, DSM-adherent BD. Irritability that waxes and wanes spontaneously or in conjunction with other episodic changes in energy or sleep is much more suggestive of a mood disorder than other pathology.

While calls to include severe, chronic irritability as a developmental type of BD among youth have waned, substantial data have accrued about repeated brief discrete episodes of

hypomania for less than four days as part of the BD spectrum. As among adults,(63) youth manifest cyclothymic disorder(64) and episodic OS-BRD, as well as BD-I and BD-II. However, as described below, youth with brief but well defined episodes of mania or hypomania are at very high risk to switch into BD-I or BD-II (particularly if they have family history of BD)(65), and they have as much psychosocial impairment, suicidality, comorbidity (e.g, substance abuse), and family history of BD as those with BD-I.(66) Less research has specifically addressed CycD, which is often subsumed within the BD-NOS category due to lack of operationalized criteria.(1, 64, 67)

Ultra-rapid or "ultradian" cycling also has been associated with pediatric (as well as adult) BD.(68) Although youth with BD, particularly younger children, often have more mood fluctuations than adults, it appears that "ultra-rapid cycles" describes mood fluctuation within an episode, and are not themselves distinct episodes.(69)

Similar to adult BD, PBD has extensive comorbidity, both in representative epidemiologic studies with largely untreated samples,(17, 70, 71) as well as clinical samples.(72) With the exception of developmental disorders like ADHD and autism spectrum disorders, the patterns of comorbidity are broadly consistent between youth and adult presentations.(72, 73) Apparent differences may partly reflect limited assessment of ADHD and autism spectrum disorders in adult samples rather than a true difference in comorbidities between these age groups, although some studies also suggest an association between ADHD and earlier age of onset of bipolar illness in adult samples.(74, 75) The presence of comorbid disorders worsens the course and outcome of PBD, indicating the need for their identification and treatment. When determining comorbid diagnoses, it is important not to "double-count" overlapping diagnostic symptoms (e.g., hyperactivity in ADHD, irritability in multiple disorders), as this leads to

artificially high rates of comorbidity. Identifying discrete mood episodes and ensuring that overlapping symptoms are (i) over and above what can be expected from the individual's baseline, and (ii) concurrent with mood episodes helps disentangle clinical presentations. Conversely, symptoms that persist in periods of euthymia suggest a non-mood etiology, and thus a "true" comorbidity. Finally, there is increasing evidence that medical comorbidity is relevant to PBD, both in terms of the association of physical health characteristics such as obesity with suicidality, neurocognition, and other markers of psychiatric symptom burden, and in terms of future premature cardiovascular disease(76-80). Medical comorbidity is closely related to both the mood symptoms and related lifestyle behaviors such as sedentary lifestyle and binge-eating in PBD(81, 82).

Differential Diagnosis

Diagnosing PBD requires changes in mood and behavior that are uncharacteristic of the individual and more extreme than developmentally appropriate, persist long enough to satisfy duration criteria, and have a clear impact on functioning. If comorbid disorders are present, mood symptoms need to be above and beyond the regular symptoms for the other disorder. For example, if symptoms of ADHD get worse episodically, and during these episodes the youth presents symptoms more specific to mania (e.g., decrease need for sleep), a PBD diagnosis should be considered. Symptom sequence may help differentiate BD from some other disorders: a teen with BD might first experience symptoms of hypomania and depression and then begin using substances, in contrast to another teen who experimented with drugs first and then began showing irritability. However, it can be difficult to separate onset of a comorbid disorder from onset of manic/hypomanic symptoms.

Although the new and controversial DSM-5 diagnosis, disruptive mood dysregulation Disorder (DMDD), cannot formally be diagnosed if the youth has BD,(83) the phenotype commonly overlaps with all BD subtypes(61, 84, 85) as well as other conditions, particularly oppositional defiant disorder (ODD)(86, 87) Thus one must evaluate the potential presence of BD even if DMDD is identified, and vice versa. The reliability of DMDD diagnoses was low in the DSM-5 field trials, suggesting that it may be challenging to accurately identify clinically.

Course

Multiple longitudinal studies have prospectively followed cohorts of youths for four or more years. Consistent findings include (a) high rates of progression from BD-NOS or CycD into BD-I or BD-II (e.g. 43%),(65) particularly in youth with family history of BD; (b) high rates of recovery from episodes, particularly with treatment (e.g. 81.5%);(88, 89) (c) high rates of recurrence into depression, hypomania, or mania (e.g. 62.5%);(65, 88, 90, 91) and (d) patterns of comorbidity(92) and treatment response congruent with adult BD.(93) The prodrome of BD-I or BD-II, often identified retrospectively in adult studies, commonly involves attenuated mood symptoms; and sleep disturbance may be a marker clinically (see reference for detailed discussion of prodrome).(94)

Limitations, gaps, and future directions

Remaining controversies include whether ADHD might be a prodrome for BD. Some studies suggest that ADHD might be a prodrome,(95, 96) although some used interviews that blurred the distinction between mood episodes and more chronic presentations.(45) Longitudinal studies of ADHD cohorts tend to find no or only small increases in risk of BD.(97)

Adding the DMDD diagnosis to DSM-5 created several gaps in terms of evidence-based assessment methods to differentiate DMDD from mood disorders, and lack of clarity regarding effective treatments. DMDD has its own definitional problems, as irritability includes both mood (often loses temper) and behavior (what happens when temper is lost).(47) The next version of ICD will not add DMDD as a diagnosis, instead making a mood disturbance specifier for oppositional-defiant disorder.(98) Research needs to evaluate the relative effectiveness of psychosocial (e.g., parent training; emotion regulation strategies) and pharmacological interventions for DMDD.(62, 99) Longitudinal data also raise interesting questions about the possibility of remission of DMDD and bipolar disorders (56, 100), a topic that warrants further study.

5. Measurement

Established findings and consensus

There has been a large increase in the number of scales available and supported by data to measure different aspects of PBD. Myths ready for retirement include: (a) there is no validated rating scale or checklist for assessing manic symptoms in youth, (b) a profile of scores on the Child Behavior Checklist (CBCL)(52) can be used as a proxy for a diagnosis of PBD, and (c) black or white thinking about the value of a particular informant perspective in the evaluation of PBD (see Table 1). Common (and mistaken) beliefs include “teacher report is essential for confirming a diagnosis of mania,” versus “teacher report is useless in the evaluation of PBD”, or “parents’ perspective is always right” versus “parents’ perspective is hopelessly contaminated by their own mood or agenda.”

Current State of Assessment

The current generation of practitioners completed their training before the bulk of research about PBD was available. Consequently, agreement between clinicians about the presence or absence of PBD in a particular case is poor.(101, 102) Agreement also tends to be worse around cyclothymic disorder and OS-BRD(23, 103) which is unfortunate given that these may be more common than BD-I.(25, 67)

Cross-Informant Report on Checklists

Multiple studies have evaluated parent, youth, and teacher report on both broad symptom checklists, such as the Achenbach System of Empirically Based Assessment,(52) along with manic symptom scales. Agreement between informants on ratings of the youth's mood symptoms tends to be only "fair," i.e., in the *r*=.2 to .3 range, consistent with meta-analyses of agreement about youth mood and behavior in general.(104)

Checklists can detect cases needing more in-depth evaluation for potential PBD. A recent meta-analysis found 63 effect sizes--38 based on caregiver, 14 on youth, and 11 on teacher report, with 8 checklists providing at least two different effect sizes. Teacher and youth reports had medium effect sizes, and parent/caregiver reports had the largest effect sizes. The Achenbach Externalizing scale outperformed the putative "bipolar" profile, consistent with findings that the "bipolar" profile is not specific to PBD.(105, 106) Manic symptom scales fared better at identifying PBD, with three top tier options: The Parent General Behavior Inventory(107) and its 10-item mania short form,(108) the Child Mania Rating Scale(109) and its 10 item short form,(110) and the parent version of the Mood Disorder Questionnaire.(111)

These scales are not accurate enough to justify their use as universal screening devices or as substitutes for a (semi) structured diagnostic interview. However, they can change the

probability of a PBD diagnosis within an evidence-based medicine or Bayesian decision-making framework(112, 113) and substantially improve the accuracy of clinical interpretation and agreement about next clinical action.(103, 113) Some checklists have also shown sensitivity to treatment effects in masked randomized controlled trials (RCTs), with effect sizes equal to those based on direct interview of the youth and primary caregiver.(114, 115) Checklists can improve diagnostic decision making in a range of clinical settings, as well as measuring treatment response.(91, 101-103)

Diagnostic & Severity Interviews

Semi- or structured diagnostic interviews that systematically evaluate mood symptoms remain the best available method to establish PBD diagnoses(53, 116) as well as symptom severity. The Young Mania Rating Scale (YMRS)(117) and Child Depression Rating Scale Revised(118) have been the industry standard interviews to quantify severity. Newer alternatives were designed for pediatric patients, with developmentally appropriate anchors and complete coverage of DSM mood symptoms.(119) Psychometric differences between severity interviews are small,(120, 121) so the choice is more conceptual than statistical. Interview length and training requirements are barriers to routine clinical use.(45) More structured methods are faster and easier to use consistently, and are surprisingly popular with patients.(122) It is important to check for mood episodes in the context of developmental history at the outset of the interview. Few methods provide a clear algorithm for CycD or OS-BRD – a key omission given the data about prevalence and burden.

Risk Factors as Part of Clinical Evaluation

Risk factors inform the initial diagnostic evaluation process, and may guide treatment selection. Family history of mood disorders--and BD in particular—is the best-validated risk factor, recommended for routine clinical evaluation, while keeping in mind that the majority of youth with a family history will not necessarily develop BD. Brief screening tools make adding family history clinically feasible.(123) High expressed emotion (EE, i.e., criticism, hostility, emotional overinvolvement) and high family conflict are risk factors for treatment drop-out and more rapid relapse.(91) High EE families may show larger responses to family-focused psychotherapeutic interventions.(124)

Limitations, gaps, and future directions

Although considerable advances have been made in the use of rating scales, checklists, and structured diagnostic interviews, little work has been done with neurocognitive or neuroimaging methods using clinically generalizable comparison groups to establish whether these methods have diagnostic specificity. Productive next steps in assessment research would be to examine hybrid batteries that combine checklists and neurocognitive measures, biomarkers, or imaging to test incremental validity (i.e., the degree to which each measure improves diagnostic accuracy) in order to guide the most cost-effective test sequences. Better assessment of developmental phenomenology would be valuable to clarify prodromal presentations and trajectories. Structured interviews could be redesigned to better capture duration, potential prodrome, and trajectories. Rapid changes in Internet-based and smartphone delivery of clinical assessments need to be integrated with traditional assessment and treatment. Finally, feasibility, acceptability and utility of translation of research tools into real-world measurement based care need to be studied.

6. Pharmacological Treatment

Established findings and consensus:

This section summarizes extant literature about pharmacologic treatment of PBD, emphasizing RCTs. For additional detail, the reader is referred to recent reviews on this topic.(38, 125-130)

Manic/Mixed Episodes

Second-generation antipsychotics (SGAs) approved by the United States Food and Drug Administration (FDA) for the treatment of acute mania and/or mixed mania in children and adolescents (10-17 years) include risperidone, aripiprazole and quetiapine, olanzapine, and asenapine (13–17)(http://www.accessdata.fda.gov/scripts/cder/daf/). Lithium has FDA-indication for the treatment and recurrence prevention of mania in youths ages 12 and older, bolstered by a recently published positive 8-week RCT for youths 7-17 years old with BD-I manic/mixed episodes.(131) In that study, change in mania symptom scores was significantly larger in lithium-treated participants, as was global improvement at week 8, compared to placebo-treated participants.

A large (n=153) 8-week NIMH-funded RCT compared lithium versus divalproex versus placebo in youths ages 7-17 years with BD-I mania.(128) Participants randomized to divalproex had significantly larger reduction in YMRS scores (ΔM=8.3) from baseline compared to those randomized to placebo (ΔM=5.3) (p=0.04). There was not a statistically significant difference in YMRS scores for subjects randomized to lithium (7.2) compared to placebo (p=0.19), or divalproex versus lithium (p=0.35). However, another 4-weel RCT of divalproex extended-

release was negative when comparing an active group (n=74) to placebo (n=70).(132) In this investigation, treatment with divalproex ER promoted a mean reduction of 8.8 points in the YMRS, and the placebo group presented a mean reduction of mania of 7.9 points (p=0.6). In an open extension of this trial with divalproex ER, where only 26 of 66 patients completed a 6-month follow-up, the mean YMRS score decreased by 2.2 points from a baseline of 20.3

An early meta-analysis on the treatment of PBD (*N*=2,666 participants across 46 trials) reported that SGAs were highly efficacious and superior to the modest anti-manic effects for traditional mood stabilizers agents, such as lithium carbonate, divalproex sodium, and carbamazepine, when used as monotherapy.(130) Another meta-analysis of double-masked placebo-controlled RCTs of BD-I mania among youth (*n*=1609) and adults (*n*=6501) found that SGAs were relatively more efficacious but more metabolically burdensome compared to traditional mood stabilizers, among youth as compared to adults.(133) However, these meta-analyses predated recent studies supporting the efficacy of lithium.

The anticonvulsants divalproex sodium and carbamazepine have not fared well head-to-head with SGAs. In two meta-analyses, treatment effect was less robust with anticonvulsants than SGAs.105, 106 An RCT of divalproex extended release was negative(132), as was a large RCT of oxcarbazepine (111), and a topiramate RCT in youth was interrupted prior to its completion due to negative results in adult studies; it failed to show efficacy in youth given inadequate power(134). A study of 10 outpatients with BD (11-17 years old) whose weight increased by over 5% during treatment with mood-stabilizer or antipsychotic monotherapy were switched to topiramate; reductions in manic symptoms and weight were observed.(134, 135)

In the "Treatment of Early Age Mania" 8-week trial, which included 290 youths ages 6-15 years with BD-I manic or mixed episodes, response rates were 68% for risperidone, 35% for lithium, and 24% for divalproex sodium.(136) The advantage of risperidone vs. lithium was greater for youth with ADHD (vs. non-ADHD) and non-obese (vs. obese) youth.(137) However, rates of comorbid ADHD in this study were over 90%, limiting power for ADHD vs. no-ADHD comparisons, and some sites showed similar response rates for risperidone and lithium. Concerns have been raised regarding several characteristics in this sample, including prolonged episodes, very early childhood onset, and high rates of rapid cycling, constraining comparisons with adult studies.(138)

In two meta-analyses, treatment effect was less robust with anticonvulsants than SGAs. A recent meta-analysis on the treatment of PBD (*N*=2,666 participants across 46 trials) reported modest effects for traditional antimanic agents, such as lithium carbonate, divalproex sodium, and carbamazepine, when used as monotherapy.(130) Another meta-analysis of double-masked placebo-controlled RCTs of BD-I mania among youth (*n*=1609) and adults (*n*=6501) found that SGAs were relatively more efficacious but more metabolically burdensome compared to traditional mood stabilizers among youth, whereas these agents were more similar among adults.(133) However, these meta-analyses predated recent studies supporting the efficacy of lithium.

Bipolar Depression

The combination of olanzapine and fluoxetine has an FDA indication for BD depression in youth aged 10-17 years old.(139) There have been two negative RCTs of quetiapine for bipolar depression.(140, 141) In a sample of 193 adolescents (10-17yo) with BP-I or II who

received quetiapine or placebo for 8 weeks.(128) Although nonsignificant differences were observed between the responses in the placebo and quetiapine groups (p=0.63), high rates of response were observed in both groups (placebo: 55%, and quetiapine XR: 63%).(128) A smaller trial of 32 adolescents (12-18yo) with BP-I where subjects were randomized for 8 weeks to placebo (n=15) or quetiapine (n=17) revealed no statistically significant differences in response rates between the placebo (67%) versus quetiapine (71%). (129) Positive preliminary open trials(142, 143) or chart reviews(144) of lithium and lamotrigine warrant future RCTs. However, high placebo response rates in depression studies require larger samples than mania trials or blinded placebo lead-in. Although the precise frequency of antidepressant induced mania is uncertain,(145, 146) practice parameters and guidelines suggest avoiding antidepressant monotherapy; this approach is supported by pharmaco-epidemiologic data.(147)

Maintenance/continuation Treatment

There have been few maintenance/continuation treatment studies in youth, most of which have been previously reviewed.(126) An early observational study of continuation treatment with lithium found increased risk of relapse among adolescents who were not treated with lithium following hospitalization for mania.(148) A subsequent study of children and adolescents with BD who had been stabilized on the combination of lithium and divalproex found similar survival time to recurrence among those randomized to continuation treatment with monotherapy with lithium or divalproex.(149) In a larger continuation study of 226 youth with BD (mean duration 124.4 days), YMRS scores decreased a further 12.4 points.(150) In a 72-week maintenance study of 96 outpatient children, 4-9 years old, with BPSD who had been stabilized on aripiprazole (mean dose 6.4mg) were randomized to continuation with

aripiprazole or placebo (*n*=30/group).(151) Although children randomized to aripiprazole, versus placebo, were enrolled significantly longer until time to discontinuation for a mood event or for any reason, the study was constrained by high drop-out rates within the first 4 weeks (50% for aripiprazole group, 90% for placebo group), understood by the authors as a nocebo effect. No significant between-group treatment effects on symptoms rating or changes over time were observed for mania, depression, general impression, or global assessment. Another placebo-controlled continuation study of aripiprazole (10mg or 30mg) in youths (10-17 years) with manic/mixed episodes followed participants for 26 weeks under double-blind conditions after a 4-week acute treatment phase.(152) For both aripiprazole dosages, there were greater reductions in YMRS symptoms (in LOCF analyses only) and time to all-cause discontinuation was longer for both aripiprazole dosages compared to placebo. There were also higher response rates, greater improvements in global functioning, and greater reductions in CGI bipolar severity for each of the aripiprazole groups vs. placebo. Another recent study of 301 children and adolescents with BD-I stabilized for at least 6 weeks on adjunctive lamotrigine, in combination with up to two mood stabilizers or antipsychotics, randomized participants to 36-weeks of either continuation treatment with lamotrigine or placebo.(153) Although the primary analysis was negative, continuation lamotrigine was superior to placebo (hazard ratio 0.46) in 13-17 year-olds, but not 10-12 year-olds (hazard ratio 0.94). Although reasons for this discrepancy are uncertain, it may relate to higher rates of ADHD in the younger group. Finally, a 50-week open-label, flexible-dose extension study of 321 youth 10-17 years old with BP-I (lead-in study treatment: placebo, n=80; asenapine, n=241) reported that: i) there was a mean 9.2 point reduction in YMRS at week 50; ii) 79.2% were considered responders based on 50%

reduction in YMRS relative to acute trial baseline; iii) somnolence/sedation/hypersomnia (42.4%) and significant weight gain (34.8%) were very common.(154)

Comorbidity

Positive results have been reported regarding the treatment of comorbid ADHD with mixed amphetamine salts and methylphenidate, albeit in modest-sized samples, particularly in euthymic youth.(38, 155, 156) Aripiprazole did not differ from placebo in ADHD symptoms reduction.(157) Preliminary findings from open trials and case reports suggest promise for adjunctive atomoxetine.(158) Although stimulants, as well as antidepressants, hold some risk of precipitating mania, precise estimates of this risk are lacking, both with and without ongoing mood stabilizer cotreatment.(145) A single small RCT found that lithium improved mood symptoms and comorbid substance use disorder among adolescents with, or at risk for, BD.(159).

Nutritional interventions

Four open-label nutritional trials, three of Ω3 monotherapy (n=3) and one of a commercially available multinutrient, in youth with BPSD provide preliminary evidence of potential benefits in terms of manic and depressive symptoms, global functioning, and parent-rated internalizing and externalizing behaviors.(160-162) A 12-week pilot RCT (N=23 youth with BP-NOS or cyclothymic disorder) found that the combination of Ω3 and psychoeducation was superior to placebo and active monitoring.(163) An RCT of flax seed oil (alpha-linolenic acid, ALA) in youth with BPI/BPII was negative.(164)

Limitations, gaps, and future directions:

Positive RCTs for maintenance treatment and bipolar depression are lacking, although preliminary positive open trials hold promise. Pharmacologic treatment of comorbidities other than ADHD is another gap. Given concerns about heterogeneity of longitudinal course, it would be helpful to examine whether subtype of bipolar disorder or age of onset moderate treatment response. Future studies should include neuroimaging, neurocognition, and peripheral biomarkers as moderators and predictors of treatment response. Large-scale RCTs of nutritional interventions are warranted, based on positive pilot RCTs and open-label trials. Studies concentrating on CycD and OS-BRD are crucial to address the need for titrated and evidence-based options, along with more masked maintenance studies to look at altering trajectories, and head-to-head trials and trials of combinations with non-pharmacological treatments. Although systematically addressing the topic of offspring of parents with BD was beyond the scope of this article, it is important to note that there is also a need for large-scale RCTs examining the relative efficacy, tolerability, and safety of antidepressants vs. mood-stabilizers for anxiety and/or depression, and the efficacy, tolerability, and safety of stimulants for ADHD, among BD offspring.

7. Psychosocial Treatments

Established findings and consensus:

Adult psychotherapy trials provide substantial evidence for the effectiveness of family-focused therapy (FFT),(165) group psychoeducation,(166-168) and interpersonal and social rhythm therapy(169) in improving symptoms, reducing rates of recurrence, and hastening recovery in adults with BD. In recent years, an accumulating body of evidence similarly supports

the use of manualized psychotherapies for the treatment of PBD. A recent review highlighted 13 unique studies(170) and 3 studies published since that review further strengthen the evidence-base;(171-174) whereas one additional study offers mixed evidence.(175) The category of family psychoeducation plus skill-building can be considered as a *well-established* treatment, meaning that two or more research groups have, via independent RCTs, demonstrated efficacy.(176) Dialectical behavior therapy(171) can be considered *possibly efficacious*—based on a single RCT or multiple studies by the same group, while interpersonal and social rhythm therapy(177) remains *experimental* in youths at this time. Effectiveness trials suggest family psychoeducation plus skill building approaches have excellent acceptability and sustainability in community settings.(178, 179)

Treatment *mediator analyses* suggest that psychoeducation leads families to improve the quality of services they utilize, mediated by parental treatment beliefs; improved quality of services, in turn, mediates improved outcomes.(180) Improved parenting skills and coping, family flexibility and family positive reframing are linked with improved mood and global functioning in youth with PBD.(181) Treatment *moderators* include greater youth impairment(182) and high family expressed emotion,(124) along with comorbid disorders, youth age, and family SES. *Predictors* of better treatment response include greater impairment, more stress/trauma history for the child, less Cluster B personality symptoms in parents,(182) and comorbid anxiety disorders.(132)

With regard to secondary outcomes other than mood, family psychoeducation plus skill building are also associated with a reduction in behavioral symptoms.(183) In an open trial of an adaptation of family psychoeducation and skill building, benefits were observed for

adolescents with BD and comorbid substance use disorders.(184) While no dismantling studies have been conducted, therapeutic ingredients common to the psychotherapy category *family psychoeducation and skill building* should be used. These include family involvement; psychoeducation about etiology, symptoms, course, medications, risk and protective factors, and effective treatment of BD; skill building (especially communication, problem-solving, and emotion regulation skills); and relapse and recurrence prevention.(170)

In regard to prevention, or delay of onset, two RCTs have examined the impact of family psychoeducation plus skill building in youth at high-risk for developing BD. Youth who received FFT had more rapid recovery from their initial mood symptoms, experienced more weeks in remission, and had lower YMRS scores over one year compared to youth who received enhanced care.(185) In a second study, youth with depression and transient manic symptoms were four times less likely to convert to BPSD at 12-month follow-up if they received MF-PEP plus treatment-as-usual (TAU) compared to the group who received only TAU.(186)

Limitations, gaps, and future directions:

More work needs to (a) determine the impact of low-risk interventions (e.g., psychosocial treatments, nutritional interventions) in preventing or delaying onset of BD in high-risk youth; (b) test psychotherapies in diverse populations, including different SES and cultural backgrounds; (c) determine what modifications are appropriate based on age or treatment format (e.g., group or individual/family); (d) determine the impact of psychotherapy on functional and quality of life outcomes as well as symptoms; (e) develop efficient ways to train large numbers of clinicians in these treatments, (f) identify mechanisms of change and

essential treatment components;(170) (g) examine the potential benefits of smartphone or Internet-based delivery; (h) evaluate combinations of pharmacotherapy and psychotherapy; and (i) determine how best to disseminate manual-based psychotherapies into healthcare settings.

8. Neuroimaging and Neurocognition

Established findings and consensus:

Prevailing pathophysiologic models of BD implicate abnormalities in brain regions that regulate emotion and attention, namely the emotional control network (ECN).(187) The ECN is comprised of ventrolateral and ventromedial prefrontal networks, which modulate the limbic system, specifically the amygdala, in conjunction with subcortical nuclei, such as thalamus and striatum(187-189). Increasing evidence suggests there are anatomical, neurochemical, functional and cognitive abnormalities within the ECN in PBD.(188, 190) Pathophysiological abnormalities underlying other cognitive functions that are altered in BD, such as reward processing, have also been studied.(191)

Neuroimaging

Brain structure: Within the ECN, the amygdala plays a central role in emotional regulation. Two meta-analyses of magnetic resonance imaging (MRI) studies reported that youth with PBD present with smaller amygdala volumes compared with controls.(192, 193) One prospective study that evaluated youth after their first manic episode showed that amygdala volumes failed to show a normal increase with aging in patients, whereas this did not occur in controls or in youth with ADHD, suggesting that a hampered neurodevelopment of amygdala

may underlie the dysfunctional emotional processing present in the ventral-limbic pathway.(194) Diffusion tensor imaging (DTI) studies have investigated abnormalities in white matter microstructure of youth with PBD. Preliminary findings suggest the presence of abnormal white matter microstructure in superior frontal regions,(195, 196) and inferior/ventral frontal areas, such as orbitofrontal or anterior cingulate cortex, and anterior regions of the corpus callosum(197-201) compared to controls. One study found even greater reduction in white matter integrity in the anterior limb of the internal capsule in PBD versus adult BD.(202) Most of these studies have very small sample sizes, but together, they are consistent with a hypothesis of structural connectivity deficits between prefrontal-subcortical areas that underlie the prefrontal-limbic dysfunction in PBD.

Brain function: Meta-analyses of over 20 task-based functional MRI (fMRI) studies with approximately 500 youth concluded that BD involves hypoactivation of prefrontal areas and hyperactivation of limbic areas.(203, 204) Weigbreit et al (2014) included included mostly emotional (emotional face processing task) than non-emotional (or cognitive tasks) whereas Lee et al (2014) did not discriminate effects of emotional versus cognitive tasks. PBD presents with greater activation in right amygdala, parahippocampal gyrus, and left putamen, and lower activation in the right ventrolateral and dorsolateral prefrontal cortices compared with controls in paradigms that involve emotional stimuli.(203, 204) These findings suggest that prefrontal regions are unable to modulate hyperactive limbic regions,(204) either due to a primary prefrontal dysfunction or to altered connectivity between prefrontal and limbic regions. Studies using non-emotional tasks (e.g. reversal learning and reward anticipation) also showed abnormal functional activity of prefrontal areas, such as dorsolateral prefrontal cortex, parietal

regions, such as temporal gyrus, and subcortical regions, such as thalamus during processing of the tasks.(205-207) fMRI studies using tasks of attention and response inhibition have also found that prefrontal areas involved with attention and inhibitory control (namely ventrolateral prefrontal cortex) are hypoactive while processing a continuous performance task in patients with PBD and comorbid ADHD, while posterior parietal and temporal areas were hyperactive, possibly as a compensatory mechanism.(208) Other studies using continuous performance task and response inhibition also have found underactivation of ventrolateral prefrontal cortex.(209, 210) The few resting state fMRI studies in PBD show that youth with PBD present with fronto-temporal, amygdala-hippocampus and amygdala-precuneus functional connectivity alterations(211-213), with similar alterations observed during bipolar depression.(214) Together, these studies suggest that PBD is characterized by abnormal prefrontal-limbic functional connectivity in the processing of emotion, attention, and reward. Although still too preliminary to allow any definitive conclusions about the neurophysiology of PBD, these findings converge with adult BD findings.

Brain chemistry: Proton magnetic resonance spectroscopy studies are particularly important to help understand two current neurobiological hypotheses of BD, e.g., glutamatergic dysfunction and mitochondrial dysfunction or energy metabolism dysfunction. Several studies in in PBD have shown abnormalities in glutamate or glutamine levels in prefrontal brain areas (215, 216). Abnormal levels of metabolites that are considered to be biomarkers of mitochondrial dysfunction or cell energy metabolism, such as decreased N-acetyl-aspartate or increased myo-inositol levels, were found in dorsal and ventral areas of the prefrontal cortex in PBD (217-225).

Although very valuable given the possibility of *in vivo* measurement of metabolites that might relate to pathophysiological processes of neuronal integrity/viability, glutamatergic neurotransmission, and cell energy metabolism, the exact meaning of these results is poorly understood, partly because they are difficult to replicate or to predict. For instance, although several proton spectroscopy studies reported positive results for specific metabolite differences between patients and controls (e.g., N-acetyl-aspartate or glutamine)(216, 221, 224, 225), within the same experiment, results are often negative for other metabolites (e.g., creatine, myo-inositol, choline)(216).

Neuroimaging in relation to treatment

There is a preliminary literature regarding neuroimaging studies in relation to treatment of PBD. For instance, an association between change in prefrontal glutamate concentrations and change in manic symptoms was reported in patients who achieved remission of mania after treatment with divalproex sodium.(226) Remission of mania after olanzapine treatment was associated with an increase in ventromedial prefrontal N-acetyl aspartate and choline levels.(227) Quetiapine treatment for bipolar depression may lead to decreased neural activity in left occipital cortex, and increased neural activity in left insula, left cerebellum, and right ventrolateral prefrontal cortex during performance of a face emotion recognition task.(228) Treatment of mania with ziprasidone was associated with increase in activation in the right ventrolateral prefrontal cortex in response to a sustained attention task, which suggests that ziprasidone antimanic effect is associated to an improved prefrontal modulation of emotional regulation.(229) Carbamazepine treatment of mania also was associated with increased activation in Brodmann area 10 of the right prefrontal cortex in a

small sample of 11 adolescents(230), further suggesting that mood stabilizers might exert its beneficial effects by improving the top-down prefrontal modulation of limbic areas. Treatment response to risperidone and divalproex sodium for mania may lead to an increased functional connectivity of amygdala within the ECN.(231) These preliminary findings offer insights regarding putative mechanisms of action of these medications. One recent study provided evidence that some psychotherapy modalities, such as family-focused therapy, improve dorsolateral prefrontal cortex activation and decrease amygdala activation in youth with mood dysregulation at familial risk for BD(232) , which is consistent with the putative treatment effects of mood stabilizers (i.e., an improved prefrontal modulation of limbic areas, or a better "top-down control"). Additional studies are necessary to better understand the physiology of treatment response and guide improved therapeutic strategies.

Neurocognition

PBD is associated with impairment in several cognitive domains.(233) A meta-analysis of 10 cognitive studies reported overall cognitive deficits in PBD (*n*=352) compared to HC (*n*=439) with mean effect sizes that are: large in in verbal memory; moderate to large in attention and working memory; moderate in executive functioning, visual perceptual skills, and visual memory; and small to moderate in motor speed, reading achievement, full scale IQ, and verbal fluency.(233) A prospective study showed that youth with PBD may exhibit a delay in cognitive development compared with controls in some cognitive domains (e.g., executive functioning and verbal memory), despite optimal pharmacological management.(234) Thus, it is essential to investigate therapeutic strategies, such as cognitive remediation(235) and/or

optimizing cardiometabolic health,(79) that might be useful to restore these cognitive deficits and improve academic, social and functional impairments in youth with PBD.

In summary, in the last two decades many neuroimaging and cognition studies demonstrate anomalous brain structure, brain function, and cognition, alongside preliminary evidence of lagging neurocognitive development in PBD, mainly relating to the ECN.

Limitations, gaps, and future directions:

Further studies are necessary to understand whether abnormal neurodevelopment is present across other brain regions and to what extent abnormal neurostructure is related to abnormal brain function, behavioral aspects of the disease, and alterations in cognitive, social and functional development. Essential questions that remain unanswered concern how these abnormalities predict clinical course or the social, academic, personal, and functional impairments present in PBD. Additionally, is largely unknown which brain abnormalities represent risk factors, resilience factors, early disease markers, or some combination of these. Studies that integrate information from different imaging modalities and and theoretical perspectives should help parse these effects. Longitudinal studies will be crucial to help to discern developmental and progressive neurophysiological aspects of PBD. Finally, future studies need to parse the independent and interactive effects of PBD in relation to treatment effects and response markers, as well as common comorbidities such as ADHD, anxiety, and substance use disorders.

9. Peripheral biomarkers

Established findings and consensus:

Numerous studies over the past decade have examined peripheral biomarkers among adults with BD, focusing most consistently on a pattern of increased inflammatory and oxidative stress markers and decreased neurotrophic markers, particularly during acute mood episodes.(236-239) Peripheral biomarkers, particularly those that fluctuate in relation to symptoms, have the potential for clinical application such as in the selection, prediction, and assessment of treatments. In contrast to the relatively broad literature on neuroimaging and neurocognition, there is a relative dearth of studies on peripheral biomarkers among youth with BD. However, in recent years there has been growing interest in this topic. Given the nascent literature, the following is a synopsis rather than a conclusive demonstration of replicated findings.

In a study of 30 adolescents with PBD, hypomanic symptoms were associated with levels of high-sensitivity c reactive protein (hsCRP). Brain derived neurotrophic factor (BDNF) and interleukin 6 (IL-6) were negatively associated with each other, and cardiovascular high-risk levels of hsCRP were observed in 40% of the sample.(240) A subsequent larger study on the topic based on 123 young adults in the Course and Outcome of Bipolar Youth study found that, controlling for comorbidity and treatment, tumor necrosis factor alpha (TNF-α) was associated with the proportion of time with psychosis, IL-6 was associated with the proportion of time with subthreshold mood symptoms and with any suicide attempt, and hsCRP was associated with maximum depression severity over the preceding 6 months.(241)

Two controlled studies of adolescents with PBD provide support for elevated inflammation. The first study (18 BD, 13 MDD, 20 healthy controls) found significantly higher levels of nuclear factor kappa beta (NFκβ) in peripheral blood mono-nuclear cells, monocytes,

and lymphocytes, higher IL-1β plasma levels, and greater TNF-α-induced elevations in NFκβ in adolescents with mood disorders than HCs.(242) The second study (40 BD, 20 HC) found elevated IL-6 and TNF-α levels among adolescents with PBD.(243)

A recent study of 30 adolescents with BD found that oxidative stress markers were lower as compared to adults with BD, and lipid hydroperoxides (LPH) levels were associated with a proxy measure of atherosclerosis but not with mood symptoms or medications.(244) A population based study of young adults found that those with BPSD, but not those with MDD, had increased protein oxidative damage compared to HCs.(245) A study of adolescents with or at risk for PBD found that adolescents with had significantly lower LPH vs. controls, with non-symptomatic adolescents at familial risk falling between the other groups.(246) Finally, a study of 29 adolescents with PBD and 25 HCs found that LPH-BDNF correlations were significantly different between adolescents with PBD and HCs, and that, among adolescents with PBD in the top half of BDNF levels, greater LPH levels were associated with poorer executive function.(247)

In an early biomarker study, platelet-derived BDNF protein and lymphocyte-derived BDNF mRNA levels were reduced among 26 medication-free youth with PBD compared to HCs; mRNA BDNF levels increased significantly in a subset of 19 participants after 8 weeks of treatment.(248) A study of 30 adolescents with BD found a significant association between BDNF levels and amygdala volumes,(249) whereas other findings from the same sample indicated no association between neurotrophic factors and hippocampal volumes.(250)

Similar to blood-based biomarkers, the literature regarding the genetics of PBD is sparse. A family-based association study found that genes coding for the serotonin transporter (SLC6A4), BDNF, and catechol-O-methyltransferase (COMT) were not significantly associated

with PBD(251), whereas a prior study based on the same sample found that 4/28 SNPs in the dopamine transporter gene (SLC6A3) were associated with PBD, of which only rs40184 remained significant after correction for multiple comparisons.(252) Another family-based association study found that two SNPs in early growth gene 3 (EGR3) were nominally significantly associated with PBD(253), as were glutamate decarboxylase 1 (GAD1)(254) and BDNF val66 alleles.(255) Most recently, a genetic study based on participants in the TEAM study found that a calcium channel, voltage-dependent, L type, alpha 1c subunit (CACNA1C) haplotype was associated with PBD. Whereas the CACNA1C rs1006737 single-nucleotide polymorphism (SNP) has been previously associated with adult BD in genome-wide association studies(256), it was the rs10848632 CACNA1C SNP that was nominal associated in SNP analyses.(257)

Limitations, gaps, and future directions:

Despite the substantial increase in research findings in this area over the past 5 years, important limitations and gaps remain. Most studies have been constrained by small samples, limited covariate modeling, and cross-sectional design. Ultimately, the clinical application of peripheral biomarkers will require that findings are significant in the heterogeneous samples in which these biomarkers would be employed, as reflected by a variety of comorbidities, different subtypes of PBD, and varying medication regimens. Studies using repeated measures afford the advantage of within-subject analyses, which mitigate the impact of heterogeneity and state-related changes. With regard to genetics, larger studies are needed, as are studies examining the link between genetic markers and intermediate phenotypes, such as neuroimaging, in PBD. In addition to these considerations, studies that incorporate biomarkers

as objective predictors, treatment targets, and or correlates of treatment response are warranted.

10. Conclusions

There has been substantial progress in the area of PBD over the past 20 years. As data have accumulated and controversy has dissipated, the field has moved past existential questions about PBD toward defining and pursuing pressing clinical and scientific priorities that remain. The overall body of evidence supports the position that perceptions about marked international and developmental differences have been overstated, albeit that additional research on these topics is warranted. Traction toward improved outcomes will be supported by continued emphasis on phenomenology, prospective clinical epidemiology, pathophysiology, measurement-based quantitative approaches including digital phenotyping, and novel therapeutics.

Despite substantial increase in consensus regarding phenomenology and epidemiology, there remain outstanding questions about the prevalence of PBD in pre-pubertal children. Whereas the existence of PBD in pre-pubertal children has long been recognized, and indeed described in Kraepelin's seminal text(258), reliable and valid estimates of epidemiologic and clinical prevalence of PBD in pre-pubertal children are lacking. With the progress that has been made, in terms of parsing PBD from chronic irritability without episodic mania/hypomania, in terms of increased recognition of PBD, and in terms of screening and diagnostic instruments, the field is now better positioned to examine this topic than it was as recently as a decade ago.

In terms of pathophysiology, it is important to consider the context of the Research

Domain Criteria (RDoC) initiative, which suggests the value of integrating dimensional liability traits alongside DSM-driven diagnoses and diagnostic criteria. In addition to all the inherent complexity of BD in adults, including differences across mood states, comorbidity, and BD subtypes, among others, research focusing on youth includes the added challenge of developmental differences. Future research should focus on age effects on the biology, manifestations, and treatment of PBD.

Future research should also focus on meaningfully integrating multiple methodologic levels of analysis. Thus far, there is a paucity of research that combines, for example, multiple neuroimaging approaches, neuroimaging and/or neurocognition with biomarkers, and/or neurobiology and clinical epidemiology. To the extent that the field can apply the large sample sizes and prospective measures of cohort studies toward improved understanding of the neurobiology of PBD, findings will become increasingly clinically and heuristically relevant.

From a treatment perspective, it will be important to begin addressing functional outcomes, rather than simply a focus on symptom reduction. Even during recovery, youth with PBD demonstrate impaired psychosocial functioning. Improved understanding of the factors underlying these impairments will allow for targeted preventive and treatment approaches. More studies with longer periods of acute treatment and maintenance studies both will help to clarify stabilization and relapse prevention. Representative *epidemiological*, not just clinical, PBD samples show very high rates of suicidality and multi-comorbidity alongside very low rates of treatment, even though “over-treatment” and “over-diagnosis” garner more attention.(259, 260) The high degree of complexity and severity of PBD, even in the relatively early years of the disease, is in part an outcome of delaying or avoiding treatment altogether. It is crucial that the

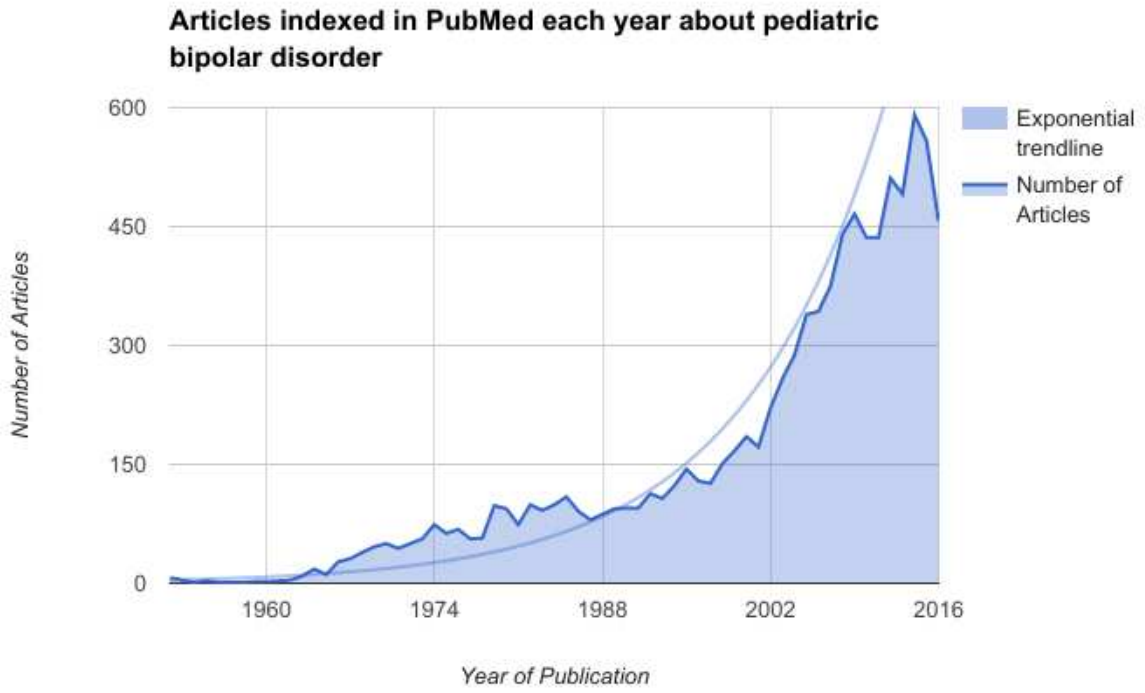
clinical and scientific community continues collaborative efforts, together with consumers, families, schools, and other stakeholders, toward public education and stigma reduction.

Finally, prevention strategies must be an area of emphasis in the decade ahead. Findings suggest that some psychotherapies and perhaps nutritional interventions might be low risk options for early stage/prodromal intervention. Here prevention not only refers to the prevention of BD, which is an important but relatively distal goal, but also to the prevention of comorbidity accumulation (e.g., substance use disorders), suicidality, treatment refractoriness, neurocognitive and functional impairment, and adverse physical health outcomes. Indeed, the physical implications of BD, particularly in terms of future cardiovascular disease, are increasingly recognized. Just as it is important for primary care providers to recognize the increased cardiovascular risk associated with PBD, it is important for our own field to begin integrating brain-body considerations in the assessment and treatment of PBD. The therapeutic and preventive potential of physical exercise for PBD, for example, is an almost entirely untouched topic.

While many questions remain unanswered, or insufficiently answered, we are hopeful that progress over the next decade will be far less constrained by controversies that, although critical in defining the directions of the field, also slowed progress and limited collaboration. At a time when clinically relevant psychiatric research faces the ironically dichotomous pressures of the RDoC era (i.e., choosing between DSM vs. RDoC), it is important to retain focus on the importance of the categorical BD diagnosis in terms of treatment selection, clinical course, and familial risk. We are optimistic that liberally applied integration strategies (i.e., dimensional as well as categorical views, neurobiology alongside clinical epidemiology, pharmacological

alongside psychosocial interventions) will best serve the needs of our field and our constituents.

Figure 1. Articles indexed in PubMed each year about pediatric bipolar disorder



Note. Search terms were ("bipolar disorder" or mania or manic) and (child or adole* or pediatric or juvenile)

http://www.ncbi.nlm.nih.gov.libproxy.lib.unc.edu/pubmed/?term=(%22bipolar+disorder%22+or+mania+or+manic+)+and+(child+or+adole*+or+pediatric+or+juvenile)

Table 1. Summary of myths, consensus, and next actions for research about pediatric bipolar disorder

Area	Myths	Data	5-year needs
1. Epidemiology	• Doesn't happen in children	• Evident in epidemiologic samples in ages 5-years and higher • Convergent adolescent data • No difference in overall or in BD-I/II rates • Inconsistent inclusion and/or definition of NOS/OS-BRD	• Include full age-range • Use consistent definition of BD-spectrum (NOS, OS-BRD) • Examine BMI, pubertal status, comorbidity
2. International perspectives	• No evidence outside of U.S.	• Evidence base includes multiple non-U.S. studies covering assessment, genetics, treatment, imaging, outcome, comorbidity	• Ensure valid translation available in multiple languages • Move toward Kessler/Harvard/Michigan-team model (WHO) using CIDI, to allow data integration and direct comparisons
3. Clinical Characteristics, Differential Diagnoses, and Course	• Adult criteria do not apply • Can forego the requirement for episodes • Predominantly chronic, and characterized by irritability without elation	• Most youth have both irritability and elation at most severe episode • Applying adult criteria yields convergent findings with adult BD • Irritable-only hypo/mania is uncommon but otherwise symptomatically similar to other PBD • Most research defines BD based on DSM, and requires episodes	• Study ADHD and related neurocognitive profiles as indicators of risk for BD • Examine comorbid DMDD-type phenotype in terms of prognostication and treatment
4. Measurement	• Screeners are not helpful • CBCL is sufficient • One type of informant is inherently superior (teacher, parent, child)	• Multiple published measures report high validity coefficients • CBCL is a poor proxy for diagnosis • Screeners can be part of evidence-	• Examine incremental value of biomarkers, imaging, cognitive testing to diagnostic accuracy • Test measures in samples that allow meaningful comparison groups to BD (e.g., ADHD, depression,

		based medicine approach to diagnosis, inform next steps	rather than healthy controls)
5. Course, Outcome, Comorbidity	• Chronic, non-episodic • No evidence of diagnostic continuity into adulthood	• When defined based on episodicity, continues to evince episodicity prospectively • Comorbidity largely dependent on age • Comorbidity by late adolescence is similar to adulthood (high rates SUD, anxiety, less ADHD) • Overlapping symptoms of mania and ADHD should not be simply double counted	• Include cognition, imaging, biomarkers in prospective studies to inform staging models • Be consistent about hierarchical exclusions (CD vs. ODD) • Examine DMDD with/without BD exclusions
6. Pharmacological treatment		• SGAs effective • Youth extra-sensitive to metabolic side-effects • Mood-stabilizers less efficacious than in adults • Stimulants for comorbid ADHD, in the context of a mood-stabilizer, are usually safe and efficacious • Adjunctive nutritional interventions show promise	• Determine if early stimulant or antidepressant treatment for ADHD and depression/anxiety, respectively, precipitate BD • Explore treatment for --bipolar depression --maintenance • Study clinical staging using low-risk interventions for high risk youth
7. Psychosocial treatment	• No validated treatments • Specific elements of treatment not relevant	• Family psychoeducation + skill building is a well-established category of psychotherapy • High EE predicts response to	• Determine core components linked to positive outcome • Match patients to treatments based on EE, etc. • Develop novel methods to access psychotherapy

		different treatments	content • Study dissemination and implementation strategies
8. Imaging and neurocognition	• No specific findings, overlap with ADHD/ODD	• Several distinguishing features, but also overlapping findings with SMD/ADHD	• Complete larger, repeated-measures studies • Use multimodal imaging
9. Biomarkers		• Few data	• Increase uptake of biomarker research • Use multimethod research (e.g., integrate imaging)

References

1. Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiological studies of bipolar disorder. Journal of Clinical Psychiatry. 2011; 72:1250-6.
2. Andrade N, Hishinuma E, McDermott J, Johnson R, Goebert D, Makini G, et al. The National Center on Indigenous Hawaiian Behavioral Health Study of Prevalence of Psychiatric Disorders in Native Hawaiian Adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 2006; 45:26-36.
3. Anselmi L, Fleitlich-Bilyk B, Menezes A, Araújo C, Rohde L. Prevalence of psychiatric disorders in a Brazilian birth cohort of 11-year-olds. Social Psychiatry and Psychiatric Epidemiology. 2010; 45:135-42.
4. Benjet C, Borges G, Medina-Mora ME, Zambrano J, Aguilar-Gaxiola S. Youth mental health in a populous city of the developing world: results from the Mexican Adolescent Mental Health Survey. Journal of Child Psychology and Psychiatry. 2009; 50:386-95.
5. Canals J, Domenech E, Carbajo G, Blade J. Prevalence of DSM-III-R and ICD-10 psychiatric disorders in a Spanish population of 18-year-olds. Acta Psychiatrica Scandinavica. 1997; 96:287-94.
6. Costello EJ, Angold A, Burns BJ, Stangl DK, Tweed DL, Erkanli A, et al. The Great Smoky Mountains Study of Youth: Goals, Design, Methods, and the Prevalence of DSM-III-R Disorders. Arch Gen Psychiatry. 1996; 53:1129-36.
7. Gould M, King R, Greenwald S, Fisher P, Schwab-Stone M, Kramer R, et al. Psychopathology associated with suicidal ideation and attempts among children and adolescents. Journal of American Academy of Child and Adolescent Psychiatry. 1998; 37:915-23.
8. Kessler R, Avenevoli S, Green J, Gruber M, Guyer M, He Y, et al. National Comorbidity Survey Replication Adolescent Supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; 48:386-99.
9. Kim-Cohen J, Caspi A, Moffitt T, Harrington H, Milne B, Poulton R. Prior Juvenile Diagnoses in Adults With Mental Disorder: Developmental Follow-Back of a Prospective-Longitudinal Cohort. Archives of General Psychiatry. 2003; 60:709-17.
10. Lewinsohn P, Klein D, Seeley J. Bipolar disorders in a community sample of older adolescents: Prevalence, phenomenology, comorbidity, and course. Journal of the American Academy of Child and Adolescent Psychiatry. 1995; 34:454-63.
11. Lynch F, Mills C, Daly I, Fitzpatrick C. Challenging times: Prevalence of psychiatric disorders and suicidal behaviours in Irish adolescents. Journal of Adolescence. 2006; 29:555-73.
12. Päären A. Hypomania spectrum disorder in adolescence: a 15-year follow-up of non-mood morbidity in adulthood. BMC Psychiatry. 2014; 14:9.
13. Pan PM, Salum GA, Gadelha A, Moriyama T, Cogo-Moreira H, Graeff-Martins AS, et al. Manic Symptoms in Youth: Dimensions, Latent Classes, and Associations With Parental Psychopathology. Journal of the American Academy of Child & Adolescent Psychiatry. 2014; 53:625-34.
14. Stringaris A, Santosh P, Leibenluft E, Goodman R. Youth meeting symptom and impairment criteria for mania-like episodes lasting less than four days: an epidemiological enquiry. Journal of child psychology and psychiatry, and allied disciplines. 2009; 51:31-8.

15. Tijssen MJ, Van Os J, Wittchen HU, Lieb R, Beesdo K, Wichers M. Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. Acta Psychiatrica Scandinavica. 2010; 122:255-66.
16. Verhulst F, Van der Ende J, Ferdinand R, Kasius M. The Prevalence of DSM-III-R Diagnoses in a National Sample of Dutch Adolescents. Archives of General Psychiatry. 1997; 54:329-36.
17. Kozloff N, Cheung AH, Schaffer A, Cairney J, Dewa CS, Veldhuizen S, et al. Bipolar disorder among adolescents and young adults: Results from an epidemiological sample. Journal of Affective Disorders. 2010; 125:350-4.
18. Oh J, Chang JG, Lee SB, Song DH, Cheon KA. Comparison of aripiprazole and other atypical antipsychotics for pediatric bipolar disorder: a retrospective chart review of efficacy and tolerability. Clin Psychopharmacol Neurosci. 2013; 11:72-9.
19. Shon SH, Joo Y, Park J, Youngstrom EA, Kim HW. Comparison of clinical characteristics of bipolar and depressive disorders in Korean clinical sample of youth: a retrospective chart review. Eur Child Adolesc Psychiatry. 2013.
20. Oh H-J, Glutting JJ, McDermott PA. An epidemiological-cohort study of DAS processing speed factor: How well does it identify concurrent achievement and behavior problems? J Psychoeduc Assess. 1999; 17:362-75.
21. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth. Archives of General Psychiatry. 2007; 64:1032-9.
22. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biological Psychiatry. 2007; 62:107-14.
23. Dubicka B, Carlson GA, Vail A, Harrington R. Prepubertal mania: Diagnostic differences between US and UK clinicians. Eur Child Adolesc Psychiatry. 2008; 17:153-61.
24. Costello EJ, Egger H, Angold A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. Journal of the American Academy of Child and Adolescent Psychiatry. 2005; 44:972-86.
25. Van Meter A, Moreira A, Youngstrom E. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. . The Journal of Clinical Psychiatry. 2011; 72:1250-6.
26. Correll CU, Hauser M, Penzner JB, Auther AM, Kafantaris V, Saito E, et al. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. Bipolar Disorders. 2014; 16:478-92.
27. Post RM, Ballenger JC, Rey AC, Bunney Jr WE. Slow and rapid onset of manic episodes: Implications for underlying biology. . Psychiatry Research. 1981; 4:229-37.
28. Bellivier F, Etain B, Malafosse A, Henry C, Kahn J-P, Elgrabli-Wajsbrot O, et al. Age at onset in bipolar I affective disorder in the USA and Europe. . The World Journal of Biological Psychiatry. 2014; 15:369-76.
29. Post RM, Luckenbaugh DA, Leverich GS, Altshuler LL, Frye MA, Suppes T, et al. Incidence of childhood-onset bipolar illness in the USA and Europe. The British Journal of Psychiatry. 2008; 192:150-1.
30. Post RM, Leverich GS, Kupka R, Keck P, McElroy S, Altshuler L, et al. Increased parental history of bipolar disorder in the United States: association with early age of onset. Acta Psychiatrica Scandinavica. 2014; 129:375-82.

31. Diler RS. Pediatric Bipolar Disorder: A Global Perspective. New York: Nova Science, 2007.
32. Masi G, Perugi G, Millepiedi S, Mucci M, Pari C, Pfanner C, et al. Clinical Implications of DSM-IV Subtyping of Bipolar Disorders in Referred Children and Adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 2007; 46:1299-306.
33. Diler RS, Uguz S, Seydaoglu G, Erol N, Avci A. Differentiating bipolar disorder in Turkish prepubertal children with attention-deficit hyperactivity disorder. Bipolar Disorders. 2007; 9:243-51.
34. Benarous X, Mikita N, Goodman R, Stringaris A. Distinct relationships between social aptitude and dimensions of manic-like symptoms in youth. Eur Child Adolesc Psychiatry. 2016; 25:831-42.
35. Masi G, Toni C, Perugi G, Mucci M, Millepiedi S, Akiskal HS. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie. 2001; 46:797-802.
36. Jairam R, Srinath S, Girimaji SC, Seshadri SP. A prospective 4-5 year follow-up of juvenile onset bipolar disorder. Bipolar Disorder. 2004; 6:386-94.
37. Srinath S, Janardhan Reddy YC, Girimaji SR, Seshadri SP, Subbakrishna DK. A prospective study of bipolar disorder in children and adolescents from India. India Acta Psychiatr Scand. 1998; 98:437-42.
38. Zeni CP, Tramontina S, Ketzer CR, Pheula GF, Rohde LA. Methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder: a randomized crossover trial. Journal of Child and Adolescent Psychopharmacology. 2009; 19:553-61.
39. Masi G, Perugi G, Millepiedi S, Mucci M, Pfanner C, Berloffa S, et al. Pharmacological response in juvenile bipolar disorder subtypes: A naturalistic retrospective examination. Psychiatry Research. 2010; 177:192-8.
40. Zeni CP, Tramontina S, Zeni TA, Coelho R, Pheula G, Bernardi J, et al. The Val66Met polymorphism at the BDNF gene does not influence Wisconsin Card Sorting Test results in children and adolescents with bipolar disorder. Revista Brasileira de Psiquiatria. 2013; 35:44-50.
41. Lauxen Peruzzolo T, Anes M, Kohmann Ade M, Souza AC, Rodrigues RB, Brun JB, et al. Correlation between Peripheral Levels of Brain-Derived Neurotrophic Factor and Hippocampal Volume in Children and Adolescents with Bipolar Disorder. Neural Plasticity. 2015; 2015:324825.
42. Zeni CP, Tramontina S, Aguiar BW, Salatino-Oliveira A, Pheula GF, Sharma A, et al. BDNF Val66Met polymorphism and peripheral protein levels in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Acta Psychiatrica Scandinavica. 2016; 134:268-74.
43. Manon HJH, Catrien GR, Marjolein W, Frank CV, Johan O, Willem AN. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disorders. 2005; 7:344-50.
44. Grigoroiu-Serbanescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V. Psychopathology in children aged 10-17 of bipolar parents: Psychopathology rate and correlates of the severity of the psychopathology. Journal of Affective Disorders. 1989; 16:167-79.

45. Galanter CA, Hundt SR, Goyal P, Le J, Fisher PW. Variability among research diagnostic interview instruments in the application of DSM-IV-TR criteria for pediatric bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2012; 51:605-21.
46. Galanter CA, Patel VL. Medical decision making: A selective review for child psychiatrists and psychologists. Journal of Child Psychology and Psychiatry. 2005; 46:675-89.
47. Carlson GA. Disruptive Mood Dysregulation Disorder: Where Did It Come from and Where Is It Going. Journal of Child and Adolescent Psychopharmacology. 2016; 26:90-3.
48. Nader EG, Kleinman A, Gomes BC, Bruscagin C, dos Santos B, Nicoletti M, et al. Negative expressed emotion best discriminates families with bipolar disorder children. . Journal of Affective Disorders. 2013; 148:418-23.
49. Teixeira AM, Kleinman A, Zanetti M, Jackowski M, Duran F, Pereira F, et al. Preserved white matter in unmedicated pediatric bipolar disorder. Neuroscience letters. 2014; 579:41-5.
50. Lee HJ, Joo Y, Youngstrom EA, Yum SY, Findling RL, Kim HW. Diagnostic validity and reliability of a Korean version of the Parent and Adolescent General Behavior Inventories. Compr Psychiatry. 2014.
51. Mesman E, Birmaher BB, Goldstein BI, Goldstein T, Derks EM, Vleeschouwer M, et al. Categorical and dimensional psychopathology in Dutch and US offspring of parents with bipolar disorder: A preliminary cross-national comparison. Journal of Affective Disorders. 2016; 205:95-102.
52. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont; 2001.
53. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry,. 1997; 36:980-8.
54. Youngstrom EA, Genzlinger JE, Egerton GA, Van Meter AR. Multivariate meta-analysis of the discriminative validity of caregiver, youth, and teacher rating scales for pediatric bipolar disorder: Mother knows best about mania. Archives of Scientific Psychology. 2015; 3:112-37.
55. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. American Journal of Psychiatry. 2003; 160:430-7.
56. Axelson DA, Birmaher B, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, et al. Concerns regarding the inclusion of temper dysregulation disorder with dysphoria in the diagnostic and statistical manual of mental disorders, fifth edition. Journal of Clinical Psychiatry. 2011; doi:10.4088/JCP.10com06220:e1-e6.
57. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. American Journal of Psychiatry. 2001; 158:303-5.
58. Carlson GA, Klein DN. How to understand divergent views on bipolar disorder in youth. Annual review of clinical psychology. 2014; 10:529-51.
59. Hunt J, Birmaher B, Leonard H, Strober M, Axelson D, Ryan N, et al. Irritability without elation in a large bipolar youth sample: frequency and clinical description. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:730-9.

60. Fonseka TM, Swampillai B, Timmins V, Scavone A, Mitchell R, Collinger KA, et al. Significance of borderline personality-spectrum symptoms among adolescents with bipolar disorder. Journal of Affective Disorders. 2015; 170:39-45.
61. Mitchell RHB, Timmins V, Collins J, Scavone A, Iskric A, Goldstein BI. Prevalence and Correlates of Disruptive Mood Dysregulation Disorder Among Adolescents with Bipolar Disorder. Journal of Child and Adolescent Psychopharmacology. 2016; 26:147-53.
62. Fristad MA, Wolfson H, Algorta GP, Youngstrom EA, Arnold LE, Birmaher B, et al. Disruptive Mood Dysregulation Disorder and Bipolar Disorder Not Otherwise Specified: Fraternal or Identical Twins? Journal of Child and Adolescent Psychopharmacology. 2016; 26:138-46.
63. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry. 2011; 68:241-51.
64. Van Meter AR, Youngstrom EA, Findling RL. Cyclothymic disorder: A critical review. Clinical Psychology Review. 2012; 32:229–43.
65. Axelson DA, Birmaher B, Strober MA, Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. Journal of the American Academy of Child & Adolescent Psychiatry. 2011; 50:1001-16.
66. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry. 2006; 63:1139-48.
67. Van Meter A, Youngstrom EA, Demeter C, Findling RL. Examining the validity of cyclothymic disorder in a youth sample: replication and extension. Journal of abnormal child psychology. 2013; 41:367-78.
68. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, et al. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology. 2000; 10:157-64.
69. Youngstrom EA, Birmaher B, Findling RL. Pediatric bipolar disorder: Validity, phenomenology, and recommendations for diagnosis Bipolar Disorders. 2008; 10:194-214.
70. Merikangas KR, He J-p, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). Journal of the American Academy of Child & Adolescent Psychiatry. 2010; 49:980-9.
71. Wittchen HU, Frohlich C, Behrendt S, Gunther A, Rehm J, Zimmermann P, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. Drug & Alcohol Dependence. 2007; 88 Suppl 1:S60-70.
72. Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar Disorders. 2016.

73. Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry. 2006; 63:175-83.
74. Gary S. Sachs, Claudia F. Baldassano, Christine J. Truman, Constance Guille. Comorbidity of Attention Deficit Hyperactivity Disorder With Early- and Late-Onset Bipolar Disorder. American Journal of Psychiatry. 2000; 157:466-8.
75. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and Diagnostic Implications of Lifetime Attention-Deficit/Hyperactivity Disorder Comorbidity in Adults with Bipolar Disorder: Data from the First 1000 STEP-BD Participants. Biological Psychiatry. 2005; 57:1467-73.
76. Goldstein BI, Blanco C, He J-P, Merikangas K. Correlates of Overweight and Obesity Among Adolescents With Bipolar Disorder in the National Comorbidity Survey–Adolescent Supplement (NCS-A). Journal of the American Academy of Child & Adolescent Psychiatry. 2016; 55:1020-6.
77. Shapiro J, Mindra S, Timmins V, Swampillai B, Scavone A, Collinger K, et al. Controlled Study of Obesity Among Adolescents with Bipolar Disorder. Journal of Child and Adolescent Psychopharmacology. 2016; 27:95-100.
78. Naiberg MR, Newton DF, Collins JE, Bowie CR, Goldstein BI. Impulsivity is associated with blood pressure and waist circumference among adolescents with bipolar disorder. Journal of Psychiatric Research. 2016; 83:230-9.
79. Naiberg MR, Newton DF, Collins JE, Dickstein DP, Bowie CR, Goldstein BI. Elevated triglycerides are associated with decreased executive function among adolescents with bipolar disorder. Acta Psychiatrica Scandinavica. 2016; 134:241-8.
80. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, et al. Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease. A Scientific Statement From the American Heart Association. 2015; 132:965-86.
81. Martin K, Woo J, Timmins V, Collins J, Islam A, Newton D, et al. Binge eating and emotional eating behaviors among adolescents and young adults with bipolar disorder. Journal of Affective Disorders. 2016; 195:88-95.
82. Jewell L, Abtan R, Scavone A, Timmins V, Swampillai B, Goldstein BI. Preliminary evidence of disparities in physical activity among adolescents with bipolar disorder. Mental Health and Physical Activity. 2015; 8:62-7.
83. APA. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
84. Axelson D, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, McCue Horwitz S, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. Journal of Clinical Psychiatry. 2012; 73:1342-50.
85. Freeman AJ, Youngstrom EA, Youngstrom JK, Findling RL. Disruptive Mood Dysregulation Disorder in a Community Mental Health Clinic: Prevalence, Comorbidity and Correlates. J Child Adolesc Psychopharmacol. 2016.

86. Copeland WE, Shanahan L, Egger H, Angold A, Costello EJ. Adult Diagnostic and Functional Outcomes of DSM-5 Disruptive Mood Dysregulation Disorder. The American journal of psychiatry. 2014; 171:668-74.
87. Mayes SD, Waxmonsky JD, Calhoun SL, Bixler EO. Disruptive Mood Dysregulation Disorder Symptoms and Association with Oppositional Defiant and Other Disorders in a General Population Child Sample. J Child Adolesc Psychopharmacol. 2016.
88. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-Year Longitudinal Course of Children and Adolescents With Bipolar Spectrum Disorders: The Course and Outcome of Bipolar Youth (COBY) Study. American Journal of Psychiatry. 2009; 166:795-804.
89. Shankman SA, Lewinsohn PM, Klein DN, Small JW, Seeley JR, Altman SE. Subthreshold conditions as precursors for full syndrome disorders: A 15-year longitudinal study of multiple diagnostic classes. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2009; 50:1485-94.
90. Wozniak J, Petty CR, Schreck M, Moses A, Faraone SV, Biederman J. High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: A four year prospective longitudinal follow-up study. Journal of Psychiatric Research. 2011; 45:1273-82.
91. Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Archives of General Psychiatry. 2008; 65:1125-33.
92. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disorders. 2005; 7:483-96.
93. McClellan J, Kowatch R, Findling RL. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Bipolar Disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2007; 46:107-25.
94. Van Meter AR, Burke C, Youngstrom EA, Faedda GL, Correll CU. The Bipolar Prodrome: Meta-Analysis of Symptom Prevalence Prior to Initial or Recurrent Mood Episodes. Journal of the American Academy of Child & Adolescent Psychiatry. 2016; 55:543-55.
95. Tillman R, Geller B. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: Rate, risk, and predictors. Development and Psychopathology. 2006; 18:1037-53.
96. Biederman J, Petty CR, Byrne D, Wong P, Wozniak J, Faraone SV. Risk for switch from unipolar to bipolar disorder in youth with ADHD: a long term prospective controlled study. J Affect Disord. 2009; 119:16-21.
97. Molina BSG, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, et al. The MTA at 8 Years. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:484-500.
98. Evans SC, Burke JD, Roberts MC, Fite PJ, Lochman JE, de la Pena FR, et al. Irritability in child and adolescent psychopathology: An integrative review for ICD-11. . Clinical Psychology Review. 2016.
99. Dickstein DP, Towbin KE, Van Der Veen JW, Rich BA, Brotman MA, Knopf L, et al. Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. Journal of Child and Adolescent Psychopharmacology. 2009; 19:61-73.

100. Cicero DC, Epler AJ, Sher KJ. Are there developmentally limited forms of bipolar disorder? Journal of Abnormal Psychology. 2009; 118:431-47.
101. Jensen-Doss A, Youngstrom EA, Youngstrom JK, Feeny NC, Findling RL. Predictors and moderators of agreement between clinical and research diagnoses for children and adolescents. Journal of Consulting & Clinical Psychology. 2014; 82:1151-62.
102. Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY. Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International Journal of Methods in Psychiatric Research. 2009; 18:169-84.
103. Jenkins MM, Youngstrom EA, Washburn JJ, Youngstrom JK. Evidence-based strategies improve assessment of pediatric bipolar disorder by community practitioners. Professional Psychology: Research and Practice. 2011; 42:121-9.
104. Achenbach TM, McConaughy SH, Howell CT. Child/Adolescent behavioral and emotional problems: Implication of cross-informant correlations for situational specificity. Psychological Bulletin. 1987; 101:213-32.
105. Althoff RR, Ayer LA, Rettew DC, Hudziak JJ. Assessment of dysregulated children using the Child Behavior Checklist: a receiver operating characteristic curve analysis. Psychological Assessment. 2010; 22:609-17.
106. Diler RS, Birmaher B, Axelson D, Goldstein B, Gill M, Strober M, et al. The Child Behavior Checklist (CBCL) and the CBCL-bipolar phenotype are not useful in diagnosing pediatric bipolar disorder. Journal of Child and Adolescent Psychopharmacology. 2009; 19:23-30.
107. Youngstrom EA, Findling RL, Danielson CK, Calabrese JR. Discriminative validity of parent report of hypomanic and depressive symptoms on the General Behavior Inventory. Psychological Assessment. 2001; 13:267-76.
108. Youngstrom EA, Frazier TW, Findling RL, Calabrese JR. Developing a ten item short form of the Parent General Behavior Inventory to assess for juvenile mania and hypomania. . Journal of Clinical Psychiatry,. 2008; 69:831-9.
109. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Birmaher B. Child mania rating scale: Development, reliability, and validity. Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45:550-60.
110. Henry DB, Pavuluri MN, Youngstrom E, Birmaher B. Accuracy of brief and full forms of the Child Mania Rating Scale. . Journal of Clinical Psychology. 2008; 64:368-81.
111. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. The American journal of psychiatry. 2006; 163:1179-86.
112. Straus SE, Glasziou P, Richardson WS, Haynes RB. Evidence-based medicine: How to practice and teach EBM (4th ed.). New York, NY: Churchill Livingstone; 2011.
113. Jenkins MM, Youngstrom EA, Youngstrom JK, Feeny NC, Findling RL. Generalizability of evidence-based assessment recommendations for pediatric bipolar disorder. Psychological Assessment. 2012; 24:269-81.
114. West AE, Celio CI, Henry DB, Pavuluri MN. Child Mania Rating Scale-Parent Version: a valid measure of symptom change due to pharmacotherapy. Journal of Affective Disorders. 2011; 128:112-9.
115. Youngstrom EA, Zhao J, Mankoski R, Forbes RA, Marcus RM, Carson W, et al. Clinical significance of treatment effects with aripiprazole versus placebo in a study of manic or mixed

episodes associated with pediatric bipolar I disorder. Journal of Child & Adolescent Psychopharmacology. 2013; 23:72-9.
116. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, et al. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. Journal of the American Academy of Child & Adolescent Psychiatry. 2001; 40:450-5.
117. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity, and sensitivity. British Journal of Psychiatry. 1978; 133:429-35.
118. Poznanski EO, Miller E, Salguero C, Kelsh RC. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. Journal of the American Academy of Child Psychiatry. 1984; 23:191-7.
119. Axelson DA, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. Journal of Child and Adolescent Psychopharmacology. 2003; 13:463-70.
120. Demeter CA, Youngstrom EA, Carlson GA, Frazier TW, Rowles BM, Lingler J, et al. Age differences in the phenomenology of pediatric bipolar disorder. Journal of Affective Disorders. 2013; 147:295-303.
121. Yee AM, Algorta GP, Youngstrom EA, Findling RL, Birmaher B, Fristad MA, et al. Unfiltered Administration of the YMRS and CDRS-R in a Clinical Sample of Children. . Journal of Clinical Child and Adolescent Psychology. 2014:1-16.
122. Suppiger A, In-Albon T, Hendriksen S, Hermann E, Margraf J, Schneider S. Acceptance of structured diagnostic interviews for mental disorders in clinical practice and research settings. Behavior Therapy. 2009; 40:272-9.
123. Algorta GP, Youngstrom EA, Phelps J, Jenkins MM, Youngstrom JK, Findling RL. An inexpensive family index of risk for mood issues improves identification of pediatric bipolar disorder. Psychological Assessment. 2013; 25:12-22.
124. Miklowitz DJ, Axelson DA, George EL, Taylor DO, Schneck CD, Sullivan AE, et al. Expressed emotion moderates the effects of family-focused treatment for bipolar adolescents. Journal of the American Academy of Child & Adolescent Psychiatry 2009; 48:643-51.
125. Peruzzolo TL, Tramontina S, Rohde LA, Zeni CP. Pharmacotherapy of bipolar disorder in children and adolescents: an update. Rev Bras Psiquiatr. 2013; 35:393-405.
126. Goldstein BI, Sassi R, Diler RS. Pharmacological Treatment of Bipolar Disorder in Children and Adolescents. Child & Adolescent Psychiatric Clinics of North America. 2012; 21:911-39.
127. Singh MK, Ketter TA, Chang KD. Atypical antipsychotics for acute manic and mixed episodes in children and adolescents with bipolar disorder. Drugs. 2010; 70:433-42.
128. Kowatch R, Findling R, Scheffer R, Stanford K. Placebo controlled trial of divalproex versus lithium for bipolar disorder. American Academy of Child and Adolescent Psychiatry 54th Annual Meeting Boston, MA, 2007.
129. Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. Journal of the American Academy of Child & Adolescent Psychiatry. 2007; 46:687-700.

130. Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry. 2011; 50:749-62.
131. Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, et al. Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study. Pediatrics. 2015; 136:885-94.
132. Wagner KD, Redden L, Kowatch RA, Wilens TE, Segal S, Chang K, et al. A Double-Blind, Randomized, Placebo-Controlled Trial of Divalproex Extended-Release in the Treatment of Bipolar Disorder in Children and Adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:519-32.
133. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disorders. 2010; 12:116-41.
134. Delbello MP, Findling RL, Kushner S, Wang D, Olson WH, Capece JA, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2005; 44:539-47.
135. Tramontina S, Zeni CP, Pheula G, Rohde LA. Topiramate in adolescents with juvenile bipolar disorder presenting weight gain due to atypical antipsychotics or mood stabilizers: an open clinical trial. Journal of Child and Adolescent Psychopharmacology. 2007; 17:129-34.
136. Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. . Archives of General Psychiatry. 2012; 69:515-28.
137. Vitiello B, Riddle MA, Yenokyan G, Axelson DA, Wagner KD, Joshi P, et al. Treatment moderators and predictors of outcome in the Treatment of Early Age Mania (TEAM) study. Journal of the American Academy of Child & Adolescent Psychiatry. 2012; 51:867-78.
138. Stringaris A. What We Can All Learn From the Treatment of Early Age Mania (TEAM) Trial. Journal of the American Academy of Child & Adolescent Psychiatry. 2012; 51:861-3.
139. Detke HC, DelBello MP, Landry J, Usher RW. Olanzapine/Fluoxetine Combination in Children and Adolescents With Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the American Academy of Child & Adolescent Psychiatry. 2015; 54:217-24.
140. Findling RL, Pathak S, Earley WR, Liu S, DelBello MP. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. Journal of Child and Adolescent Psychopharmacology. 2014d; 24:325-35.
141. DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disorder. 2009; 11:483-93.
142. Patel NC, DelBello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, et al. Open-label lithium for the treatment of adolescents with bipolar depression. Journal of the American Academy of Child & Adolescent Psychiatry. 2006; 45:289-97.

143. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. Journal of the American Academy of Child & Adolescent Psychiatry 2006; 45:298-304.
144. Shon SH, Joo Y, Lee JS, Kim HW. Lamotrigine treatment of adolescents with unipolar and bipolar depression: a retrospective chart review. J Child Adolesc Psychopharmacol. 2014; 24:285-7.
145. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? Paediatric Drugs. 2011; 13:225-43.
146. Park KJ, Shon S, Lee HJ, Joo Y, Youngstrom EA, Kim HW. Antidepressant-emergent mood switch in korean adolescents with mood disorder. Clinical neuropharmacology. 2014; 37:177-85.
147. Bhowmik D, Aparasu RR, Rajan SS, Sherer JT, Ochoa-Perez M, Chen H. Risk of Manic Switch Associated with Antidepressant Therapy in Pediatric Bipolar Depression. Journal of Child and Adolescent Psychopharmacology 2014; 24:551-61.
148. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. Journal of the American Academy of Child & Adolescent Psychiatry. 1995; 34:724-31.
149. Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, et al. Double-Blind 18-Month Trial of Lithium Versus Divalproex Maintenance Treatment in Pediatric Bipolar Disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2005; 44:409-17.
150. Redden L, DelBello M, Wagner KD, Wilens TE, Malhotra S, Wozniak P, et al. Long-Term Safety of Divalproex Sodium Extended-Release in Children and Adolescents with Bipolar I Disorder. Journal of Child and Adolescent Psychopharmacology. 2009; 19:83-9.
151. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. Journal of Clinical Psychiatry. 2012; 73:57-63.
152. Findling RL, Correll CU, Nyilas M, Forbes RA, McQuade RD, Jin N, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disorders. 2013; 15:138-49.
153. Findling RL, Chang K, Robb A, Foster VJ, Horrigan J, Krishen A, et al. Adjunctive Maintenance Lamotrigine for Pediatric Bipolar I Disorder: A Placebo-Controlled, Randomized Withdrawal Study. Journal of the American Academy of Child & Adolescent Psychiatry. 2015; 54:1020-31.e3.
154. Findling RL, Landbloom RL, Mackle M, Wu X, Snow-Adami L, Chang K, et al. Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. Pediatric Drugs. 2016; 18:367-78.
155. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. The American journal of psychiatry. 2005; 162:58-64.
156. Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and

attention-deficit/hyperactivity disorder. . Journal of the American Academy of Child & Adolescent Psychiatry 2007; 46:1445-53.
157. Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. Journal of Clinical Psychiatry. 2009; 70:756-64.
158. Hah M, Chang K. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents with bipolar disorders. . Journal of Child and Adolescent Psychopharmacology. 2005; 15:996-1004.
159. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. Journal of the American Academy of Child & Adolescent Psychiatry 1998; 37:171-8.
160. Wozniak J, Biederman J, Mick E, Waxmonsky J, Hantsoo L, Best C, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open-label trial. European Neuropsychopharmacology. 2007; 17:440-7.
161. Frazier EA, Fristad MA, Arnold LE. Feasibility of a Nutritional Supplement as Treatment for Pediatric Bipolar Spectrum Disorders. The Journal of Alternative and Complementary Medicine. 2012; 18:678-85.
162. Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain [omega]-3 polyunsaturated fatty acid supplementation. Eur J Clin Nutr. 2009; 63:1037-40.
163. Fristad MA, Young AS, Vesco AT, Nader ES, Healy KZ, Gardner W, et al. A Randomized Controlled Trial of Individual Family Psychoeducational Psychotherapy and Omega-3 Fatty Acids in Youth with Subsyndromal Bipolar Disorder. Journal of Child and Adolescent Psychopharmacology. 2015; 25:764-74.
164. Gracious BL, Chirieac MC, Costescu S, Finucane TL, Youngstrom EA, Hibbeln JR. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disorders. 2010; 12:142-54.
165. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder Lancet. 2013; 381:1672–82.
166. Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Martínez-Arán A. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of bipolar disorder: A five year follow-up. British Journal of Psychiatry. 2009; 194:260-5.
167. Bauer MS, McBride L, Williford W, Glick H, Kinosian B, Altshuler L, et al. Collaborative care for bipolar disorder: Part II. Impact on clinical outcome, function, and costs Psychiatric Services. Psychiatric Services. 2006; 57:937-45.
168. Simon GE, Ludman EJ, Bauer MS, Unutzer J, Operskalski B. Long-term effectiveness and cost of a systematic care program for bipolar disorder. Archives of General Psychiatry 2006; 63:500-8.
169. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. . Archives of General Psychiatry. 2005; 62:996-1004.
170. Fristad MA, MacPherson H. Evidence-based psychosocial treatments for bipolar disorder in youth. Journal of Clinical Child and Adolescent Psychology. 2014; 43:339-55

171. Goldstein TR, Fersch-Podrat RK, Rivera M, Axelson DA, Merranko J, Yu H, et al. Dialectical behavior therapy for adolescents with bipolar disorder: results from a pilot randomized trial. Journal of child and adolescent psychopharmacology 2015; 25:140-9.
172. Miklowitz DJ, O'Brien MP, Schlosser DA, Addington J, Candan KA, Marshall C, et al. Family-focused treatment for adolescents and young adults at high risk for psychosis: results of a randomized trial. Journal of the American Academy of Child & Adolescent Psychiatry 2014a; 53:848-58.
173. West AE, Weinstein SM, Peters AT, Katz AC, Henry DB, Cruz RA, et al. Child-and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: a randomized clinical trial. Journal of the American Academy of Child & Adolescent Psychiatry 2014; 53:1168-78.
174. Goldstein BI GT, Miklowitz DJ, Collinger KA, Axelson DA, Bukstein OG, Birmaher B. Development of integrated family -focused treatment (FFT) for adolescents with bipolar disorder and comorbid substance use disorders. NCDEU. Phoenix, AZ, 2008.
175. Miklowitz DJ, Schneck CD, George EL, Taylor DO, Sugar CS, Birmaher B, et al. A 2-year randomized trial of pharmacotherapy and family-focused treatment for adolescents with bipolar I and II disorders. American Journal of Psychiatry. 2014b; 171:658-67.
176. Fristad MA. Evidence-Based Psychotherapies and Nutritional Interventions for Children With Bipolar Spectrum Disorders and Their Families. Journal of Clinical Psychiatry. 2016; 77:e4.
177. Hlastala SA, Kotler JS, McClellan JM, McCauley EA. Interpersonal and social rhythm therapy for adolescents with bipolar disorder: Treatment development and results from an open trial. . Depression and Anxiety. 2010; 27:457-64.
178. MacPherson HA, Mackinaw-Koons B, Leffler JM, Fristad MA. Pilot Effectiveness Evaluation of Community-Based Multi-Family Psychoeducational Psychotherapy for Childhood Mood Disorders. Couple & family psychology. 2016; 5:43-59.
179. MacPherson HA, Leffler JM, Fristad MA. Implementation of Multi-Family Psychoeducational Psychotherapy for Childhood Mood Disorders in an Outpatient Community Setting. Journal of marital and family therapy. 2014; 40:193-211.
180. Mendenhall AN, Fristad MA, Early TJ. Factors influencing service utilization and mood symptom severity in children with mood disorders: Effects of multifamily psychoeducation groups (MFPGs). Journal of Consulting and Clinical Psychology. 2009; 77:463.
181. MacPherson HA, Weinstein SM, Henry DB, West AE. Mediators in the randomized trial of Child- and Family-Focused Cognitive-Behavioral Therapy for pediatric bipolar disorder. Behaviour Research and Therapy. 2016; 85:60-71.
182. MacPherson HA, Algorta GP, Mendenhall AN, Fields BW, Fristad MA. Predictors and moderators in the randomized trial of multi-family psychoeducational psychotherapy for childhood mood disorders. Journal of Clinical Child and Adolescent Psychology. 2014; 43:459-72.
183. Boylan K, MacPherson HA, Fristad MA. Examination of disruptive behavior outcomes and moderation in a randomized psychotherapy trial for mood disorders. . Journal of the American Academy of Child and Adolescent Psychiatry. 2013; 52:699-708.
184. Goldstein BI, Goldstein TR, Collinger KA, Axelson DA, Bukstein OG, Birmaher B, et al. Treatment development and feasibility study of family-focused treatment for adolescents with bipolar disorder and comorbid substance use disorders. Journal of Psychiatric Practice. 2014; 20:237-48.

185. Miklowitz DJ, Schneck CD, Singh MK, Taylor DO, George EL, Cosgrove VE, et al. Early intervention for symptomatic youth at risk for bipolar disorder: A randomized trial of family-focused therapy. Journal of the American Academy of Child and Adolescent Psychiatry. 2013; 52:121-31.
186. Nadkarni RB, Fristad MA. Clinical course of children with a depressive spectrum disorder and transient manic symptoms. . Bipolar Disorders. 2010; 12:494-503.
187. Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, et al. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disorder 2012; 14:313-25.
188. DelBello MP, Kowatch RA. Neuroimaging in pediatric bipolar disorder. Bipolar disorder in children and early adolescence: Guilford Press, 2003: 158-74.
189. Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, et al. The functional neuroanatomy of bipolar disorder: A consensus model. Bipolar Disord. 2012; 14:313-25.
190. Schneider MR, DelBello MP, McNamara RK, Strakowski SM, Adler CM. Neuroprogression in bipolar disorder. Bipolar Disorder. 2012; 14:356-74.
191. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry. 2014; 171:829-43.
192. Pfeifer JC, Welge J, Strakowski SM, Adler CM, DelBello MP. Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. Journal of the American Academy of Child & Adolescent Psychiatry 2008; 47:1289-98.
193. Usher J, Leucht S, Falkai P, Scherk H. Correlation between amygdala volume and age in bipolar disorder—a systematic review and meta-analysis of structural MRI studies. Psychiatry Research: Neuroimaging 2010; 182:2010.
194. Bitter SM, Mills NP, Adler CM, Strakowski SM, DelBello MP. Progression of amygdala volumetric abnormalities in adolescents after their first manic episode. . Journal of the American Academy of Child & Adolescent Psychiatry 2011; 50:1017-26.
195. Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. American Journal of Psychiatry. 2006; 163:322-4.
196. Frazier J, Breeze J, Papadimitriou G, Kennedy D, Hodge S, Moore C, et al. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disorders. 2007; 9:799-809.
197. Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, et al. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biological Psychiatry. 2009; 65:586-93.
198. Kafantaris V, Kingsley P, Ardekani B, Saito E, Lencz T, Lim K, et al. Lower orbital frontal white matter integrity in adolescents with bipolar I disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:79-86.
199. Saxena K, Tamm L, Walley A, Simmons A, Rollins N, Chia J, et al. A preliminary investigation of corpus callosum and anterior commissure aberrations in aggressive youth with bipolar disorders. Journal of Child and Adolescent Psychopharmacology. 2012; 22:112-9.

200. Gao W, Jiao Q, Qi R, Zhong Y, Lu D, Xiao Q, et al. Combined analyses of gray matter voxel-based morphometry and white matter tract-based spatial statistics in pediatric bipolar mania. Journal of Affective Disorders. 2013; 150:70-6.
201. James A, Hough M, James S, Burge L, Winmill L, Nijhawan S, et al. Structural brain and neuropsychometric changes associated with pediatric bipolar disorder with psychosis. Bipolar Disord. 2011; 13:16-27.
202. Lu LH, Zhou XJ, Fitzgerald J, Keedy SK, Reilly JL, Passarotti AM, et al. Microstructural abnormalities of white matter differentiate pediatric and adult-onset bipolar disorder. Bipolar Disord. 2012; 14:597-606.
203. Wegbreit E, Cushman GK, Puzia ME, Weissman AB, Kim KL, Laird AR, et al. Developmental meta-analyses of the functional neural correlates of bipolar disorder. JAMA psychiatry 2014; 71:926-35.
204. Lee MS, Anumagalla P, Talluri P, Pavuluri MN. Meta-analyses of developing brain function in high-risk and emerged bipolar disorder. Frontiers in psychiatry 2014; 5:141.
205. Dickstein DP, Finger EC, Skup M, Pine DS, Blair JR, Leibenluft E. Altered neural function in pediatric bipolar disorder during reversal learning. Bipolar Disord. 2010; 12:707-19.
206. Singh MK, Chang KD, Kelley RG, Cui X, Sherdell L, Howe ME, et al. Reward processing in adolescents with bipolar I disorder. J Am Acad Child Adolesc Psychiatry. 2013; 52:68-83.
207. Urosevic S, Luciana M, Jensen JB, Youngstrom EA, Thomas KM. Age associations with neural processing of reward anticipation in adolescents with bipolar disorders. NeuroImage Clinical. 2016; 11:476-85.
208. Adler CM, Delbello MP, Mills NP, Schmithorst V, Holland S, Strakowski SM. Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. Bipolar Disord. 2005; 7:577-88.
209. Cerullo MA, Adler CM, Lamy M, Eliassen JC, Fleck DE, Strakowski SM, et al. Differential brain activation during response inhibition in bipolar and attention-deficit hyperactivity disorders. Early Interv Psychiatry. 2009; 3:189-97.
210. Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry. 2007; 164:52-60.
211. Dickstein DP, Gorrostieta C, Ombao H, Goldberg LD, Brazel AC, Gable CJ, et al. Fronto-Temporal Spontaneous Resting State Functional Connectivity in Pediatric Bipolar Disorder. Biological Psychiatry. 2010; 68:839-46.
212. Singh MK, Kelley RG, Chang KD, Gotlib IH. Intrinsic Amygdala Functional Connectivity in Youth With Bipolar I Disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2015; 54:763-70.
213. Xiao Q, Zhong Y, Lu D, Gao W, Jiao Q, Lu G, et al. Altered regional homogeneity in pediatric bipolar disorder during manic state: a resting-state fMRI study. PloS one. 2013; 8:e57978.
214. Gao W, Jiao Q, Lu S, Zhong Y, Qi R, Lu D, et al. Alterations of regional homogeneity in pediatric bipolar depression: a resting-state fMRI study. BMC Psychiatry. 2014; 14:222.
215. Castillo M, Kwock L, Courvoisie H, Hooper SR. Proton MR spectroscopy in children with bipolar affective disorder: preliminary observations. AJNR American Journal of Neuroradiology. 2000; 21:832-8.

216. Moore CM, Frazier JA, Glod CA, Breeze JL, Dieterich M, Finn CT, et al. Glutamine and glutamate levels in children and adolescents with bipolar disorder: a 4.0-T proton magnetic resonance spectroscopy study of the anterior cingulate cortex. J Am Acad Child Adolesc Psychiatry. 2007; 46:524-34.
217. Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, et al. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology. 2001; 24:359-69.
218. Davanzo P, Yue K, Thomas MA, Belin T, Mintz J, Venkatraman TN, et al. Proton magnetic resonance spectroscopy of bipolar disorder versus intermittent explosive disorder in children and adolescents. The American Journal of Psychiatry. 2003; 160:1442-52.
219. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. J Child Adolesc Psychopharmacol. 2003; 13:545-55.
220. Chang K, Adleman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T. Decreased N-acetylaspartate in children with familial bipolar disorder. Biol Psychiatry. 2003; 53:1059-65.
221. Patel NC, DelBello MP, Cecil KM, Stanford KE, Adler CM, Strakowski SM. Temporal change in N-acetyl-aspartate concentrations in adolescents with bipolar depression treated with lithium. J Child Adolesc Psychopharmacol. 2008; 18:132-9.
222. Brambilla P, Stanley JA, Nicoletti MA, Sassi RB, Mallinger AG, Frank E, et al. 1H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients. J Affect Disord. 2005; 86:61-7.
223. Caetano SC, Olvera RL, Hatch JP, Sanches M, Chen HH, Nicoletti M, et al. Lower N-acetyl-aspartate levels in prefrontal cortices in pediatric bipolar disorder: a (1)H magnetic resonance spectroscopy study. J Am Acad Child Adolesc Psychiatry. 2011; 50:85-94.
224. Sassi RB, Stanley JA, Axelson D, Brambilla P, Nicoletti MA, Keshavan MS, et al. Reduced NAA levels in the dorsolateral prefrontal cortex of young bipolar patients. Am J Psychiatry. 2005; 162:2109-15.
225. Olvera RL, Caetano SC, Fonseca M, Nicoletti M, Stanley JA, Chen HH, et al. Low levels of N-acetyl aspartate in the left dorsolateral prefrontal cortex of pediatric bipolar patients. J Child Adolesc Psychopharmacol. 2007; 17:461-73.
226. Strawn JR, Patel NC, Chu WJ, Lee JH, Adler CM, Kim MJ, et al. Glutamatergic effects of divalproex in adolescents with mania: a proton magnetic resonance spectroscopy study. Journal of the American Academy of Child & Adolescent Psychiatry 2012; 51:642-51.
227. DelBello MP, Cecil KM, Adler CM, Daniels JP, Strakowski SM. Neurochemical effects of olanzapaine in first-hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology. 2006; 31:1264-73.
228. Diler RS, Ladouceur CD, Segreti A, Almeida JR, Birmaher B, Axelson DA, et al. Neural correlates of treatment response in depressed bipolar adolescents during emotion processing. Brain imaging and behavior 2013; 7:227-35.
229. Schneider MR, Adler CM, Whitsel R, Weber W, Mills NP, Bitter SM, et al. The effects of ziprasidone on prefrontal and amygdalar activation in manic youth with bipolar disorder.
230. Schneider MR, Klein CC, Weber W, Bitter SM, Elliott KB, Strakowski SM, et al. The effects of carbamazepine on prefrontal activation in manic youth with bipolar disorder.

231. Wegbreit E, Ellis JA, Nandam A, Fitzgerald JM, Passarotti AM, Pavuluri MN, et al. Amygdala functional connectivity predicts pharmacotherapy outcome in pediatric bipolar disorder. Brain connectivity. 2011; 1:411-22.
232. Garrett AS, Miklowitz DJ, Howe ME, Singh MK, Acquaye TK, Hawkey CG, et al. Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2015; 56:215-20.
233. Joseph MF, Frazier TW, Youngstrom EA, Soares JC. A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder." Journal of child and adolescent psychopharmacology 2008; 18:595-605.
234. Pavuluri MN, West A, Hill SK, Jindal K, Sweeney JA. Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:299-307.
235. Dickstein DP, Cushman GK, Kim KL, Weissman AB, Wegbreit E. Cognitive remediation: potential novel brain-based treatment for bipolar disorder in children and adolescents. CNS Spectrums. 2015; 20:382-90.
236. Munkholm K, BraÃ¼ner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. Journal of Psychiatric Research. 2013; 47:1119-33.
237. Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI, Frye MA, et al. Biomarkers in bipolar disorder: A positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Australian and New Zealand Journal of Psychiatry. 2013; 47:321-32.
238. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neuroscience & Biobehavioral Reviews. 2011; 35:804-17.
239. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vázquez GH, Vieta E, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33:1366-71.
240. Goldstein BI, Collinger KA, Lotrich F, Marsland AL, Gill MK, Axelson DA, et al. Preliminary findings regarding pro-inflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. Journal of Child & Adolescent Psychopharmacology. 2011; 21:479-84.
241. Goldstein BI, Lotrich F, Axelson DA, Gill MK, Hower H, Goldstein TR, et al. Inflammatory markers among adolescents and young adults with bipolar spectrum disorders. Journal of Clinical Psychiatry. 2015; 76:1556-63.
242. Miklowitz DJ, Portnoff LC, Armstrong CC, Keenan-Miller D, Breen EC, Muscatell KA, et al. Inflammatory cytokines and nuclear factor-kappa B activation in adolescents with bipolar and major depressive disorders. Psychiatry Research. 2016; 241:315-22.
243. Hatch JK, Scola G, Olowoyeye O, Collines JE, Andreazza AC, Moody A, et al. Inflammatory Markers and Brain-Derived Neurotrophic Factor as Potential Bridges Linking Bipolar Disorder and Cardiovascular Risk among Adolescents. Journal of Clinical Psychiatry. In press.
244. Hatch J, Andreazza A, Olowoyeye O, Rezin GT, Moody A, Goldstein BI. Cardiovascular and psychiatric characteristics associated with oxidative stress markers among adolescents with bipolar disorder. Journal of Psychosomatic Research. 2015; 79:222-7.

245. Magalhaes PV, Jansen K, Pinheiro RT, Colpo GD, da Motta LL, Klamt F, et al. Peripheral oxidative damage in early-stage mood disorders: a nested population-based case-control study. International Journal of Neuropsychopharmacology. 2012; 15:1043-50.
246. Scola G, McNamara RK, Croarkin PE, Leffler JM, Cullen KR, Geske JR, et al. Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder. Journal of Affective Disorders. 2016; 192:176-83.
247. Newton DF, Naiberg MR, Andreazza AC, Scola G, Dickstein DP, Goldstein BI. Association of Lipid Peroxidation and Brain-Derived Neurotrophic Factor with Executive Function in Adolescent Bipolar Disorder. Psychopharmacology. 2017; 234:647-56.
248. Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. Journal of the American Academy of Child & Adolescent Psychiatry. 2008; 47:1077-85.
249. Inal-Emiroglu FN, Karabay N, Resmi H, Guleryuz H, Baykara B, Alsen S, et al. Correlations between amygdala volumes and serum levels of BDNF and NGF as a neurobiological markerin adolescents with bipolar disorder. Journal of Affective Disorders. 2015; 182:50-6.
250. Inal-Emiroglu FN, Resmi H, Karabay N, Guleryuz H, Baykara B, Cevher N, et al. Decreased right hippocampal volumes and neuroprogression markers in adolescents with bipolar disorder. Neuropsychobiology. 2015; 71:140-8.
251. Mick E, Wozniak J, Wilens TE, Biederman J, Faraone SV. Family-based association study of the BDNF, COMT and serotonin transporter genes and DSM-IV bipolar-I disorder in children. BMC Psychiatry. 2009; 9:2-.
252. Mick E, Kim JW, Biederman J, Wozniak J, Wilens T, Spencer T, et al. Family based association study of pediatric bipolar disorder and the dopamine transporter gene (SLC6A3). American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2008; 147B:1182-5.
253. Gallitano AL, Tillman R, Dinu V, Geller B. Family-Based Association Study of Early Growth Response Gene 3 with Child Bipolar I Disorder. Journal of Affective Disorders. 2012; 138:387-96.
254. Geller B, Tillman R, Bolhofner K, Hennessy K, Cook EH. GAD1 Single Nucleotide Polymorphism Is in Linkage Disequilibrium with a Child Bipolar I Disorder Phenotype. Journal of Child and Adolescent Psychopharmacology. 2007; 18:25-9.
255. Barbara Geller, Judith A. Badner, Rebecca Tillman, Susan L. Christian, Kristine Bolhofner, Edwin H. Cook J, ,. Linkage Disequilibrium of the Brain-Derived Neurotrophic Factor Val66Met Polymorphism in Children With a Prepubertal and Early Adolescent Bipolar Disorder Phenotype. American Journal of Psychiatry. 2004; 161:1698-700.
256. Ferreira MAR, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nature genetics. 2008; 40:1056-8.
257. Croarkin PE, Luby JL, Cercy K, Geske JR, Veldic M, Simonson M, et al. Genetic risk score analysis in early-onset bipolar disorder. Journal of Clinical Psychiatry. 2017.
258. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh: E. & S. Livingstone; 1921.
259. Parens E, Johnston J. Controversies concerning the diagnosis and treatment of bipolar disorder in children. Child and Adolescent Psychiatry and Mental Health. 2010; 4:9-.
260. Mitchell PB. Bipolar disorder: the shift to overdiagnosis. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2012; 57:659-65.

Sunnybrook
HEALTH SCIENCES CENTRE

Sunnybrook Health Sciences Centre
2075 Bayview Avenue,
Toronto, ON Canada M4N 3M5
t: 416.480.6100
www.sunnybrook.ca

July 13th, 2017

Gin S. Malhi
K.N. Roy Chengappa
Samuel Gershon

Editors
Bipolar Disorders

Dear Drs Malhi, Chengappa, and Gershon,

As Chair of the International Society for Bipolar Disorders Task Force on Pediatric Bipolar Disorder, it is my pleasure to submit our revised manuscript on behalf of the Task Force and Co-Chair Dr. Eric Youngstrom for consideration of publication in the *Bipolar Disorders*. The manuscript is entitled: "*The International Society for Bipolar Disorders Task Force Report on Pediatric Bipolar Disorder: Knowledge to Date and Directions for Future Research"*. The reviewers provided helpful feedback and suggestions to which we respond, point by point, below.

The authors warrant that the material contained in the manuscript represents original work, has not been published elsewhere, and is not under consideration for publication elsewhere[1]. In the event that our work is published in the Journal the authors will transfer, assign or otherwise convey all copyright ownership to the Journal.

Sincerely,

Benjamin I. Goldstein, MD, PhD, FRCPC

Referee 1

Summary: This report by the International Society for Bipolar Disorders Task Force provides the field with a current understanding of research in pediatric bipolar disorder (BD) to date. Indeed, there has been tremendous growth and this article provides informative suggestions for future directions for research in this field. Another valuable aspect of this report is the section on dispelling myths or misguided assertions. The task force was comprised of an international group of experts, who conducted a literature review focused to build consensus and identify gaps in the literature. Please consider the following suggested changes:

1. Under the epidemiology section on page 8, authors state: " It is now well established that bipolar spectrum disorders…are common in community samples." It would be helpful here to lead with something about the more universal nature of the phenomenology (e.g. "in community samples around the world."). This sets the stage early for the section on International findings. Otherwise, this section on epidemiology should be clearly stated to relate to only the US as it appears to be written.

RESPONSE: We agree, and we have reworked the opening paragraph as suggested. Further, we added that 7 of the 17 studies were from the USA. The non-US studies come from North and South America and Europe (two from Brazil, and one each from Canada, Germany, Ireland, Mexico, Spain, Sweden, the Netherlands, and the United Kingdom.

2. International findings: under this section, considering commenting on the importance of developing culturally consistent assessment tools and translating validated scales into different languages. Since there has been some effort to do this already by Youngstrom and others, this would be a good place to add this development.

RESPONSE: We thank the reviewer for this suggestion. We have added a statement as suggested: "Translating scales into multiple languages and pursuing cross-cultural validation is accelerating progress by using consistent definitions(46), revealing considerable continuity in phenomenology.(49)"

3. Well written summary on irritability, which will be informative to clinicians, trainees, and researchers alike.

RESPONSE: Thank you!

4. On page 19 – Please spell out EE as expressed emotion. In addition, among high EE families, please specify family focused psychotherapeutic interventions. Family focused interventions may be confusing to readers unfamiliar with this treatment approach.

RESPONSE: We have made both changes as suggested, and agree that this makes things more clear for a general audience.

5. Regulation of emotional control is not the only cognitive process that is impaired in pediatric bipolar disorder. Consider attention, learning, memory, reward processing, and response inhibition to name just a few. Importantly, no mention is made on aberrant reward processing in pediatric bipolar disorder and the altered neural networks that subserve this cognitive function. The way this section is written makes it seem like the field has only conducted task-based fMRI studies using only emotional stimuli in pediatric BD.

RESPONSE: We agree, and we have addressed in revision accordingly: "Studies using non-emotional tasks (e.g. reversal learning and reward anticipation) also showed abnormal functional activity of prefrontal areas, such as dorsolateral prefrontal cortex, parietal regions, such as temporal gyrus, and subcortical regions, such as thalamus during processing of the tasks.(205-207) fMRI studies using tasks of attention and response inhibition have also found that prefrontal areas involved with attention and inhibitory control (namely ventrolateral prefrontal cortex) are hypoactive while processing a continuous performance task in patients with PBD and comorbid ADHD, while posterior parietal and temporal areas were hyperactive, possibly as a compensatory mechanism.(208) Other studies using continuous performance task and response inhibition also have found underactivation of ventrolateral prefrontal cortex.(209, 210)"

Moreover, the paragraph regarding neurocognition acknowledges meta-analytic findings of "mean effect sizes that are: large in in verbal memory; moderate to large in attention and working memory; moderate in executive functioning, visual perceptual skills, and visual memory; and small to moderate in motor speed, reading achievement, full scale IQ, and verbal fluency."

6. Consider alternative terminology to the "anterior limbic network" (ALN). It is not widely accepted to be the biosignature for bipolar disorder and may lead to confusion.

RESPONSE: We agree with the reviewer that the anterior limbic network might not be a widely accepted terminology. While there is no accepted biosignature of bipolar disorder, we have changed the "anterior limbic network" to a more neutral terminology – emotional control network (ECN).

7. Only two citations of spectroscopy (MRS) studies by one group were made in reference to pediatric bipolar disorder. Davanzo et al. and others have also characterized neurochemical response to lithium. Perhaps not entirely an important focus for this review, but consider referencing pertinent negative studies that clue the field in about the limitations of using MRS in pediatric BD.

RESPONSE: Thanks for this suggestion, we have expanded a section of spectroscopy in pediatric bipolar disorder, and now we have an entire paragraph presenting cross-

sectional spectroscopy studies in pediatric bipolar disorder, including acknowledged limitations in this area as follows:
"Although very valuable given the possibility of in vivo measurement of metabolites that might relate to pathophysiological processes of neuronal integrity/viability, glutamatergic neurotransmission, and cell energy metabolism, the exact meaning of these results is poorly understood, partly because they are difficult to replicate or to predict. For instance, although several proton spectroscopy studies reported positive results for specific metabolite differences between patients and controls (e.g., N-acetyl-aspartate or glutamine)(216, 221, 224, 225), within the same experiment, results are often negative for other metabolites (e.g., creatine, myo-inositol, choline)(216)."

8. Perhaps beyond the scope of the current review, but authors might consider adding a section on familial risk for BD as a target for prevention/early intervention. Some more elaborated discussion about risks/benefits/alternatives/future directions for use of antidepressants and stimulants would help set the stage for future studies that might clarify which youth are more likely to benefit or develop adverse side effects from these agents.

RESPONSE: We agree with the reviewer regarding the importance of this topic and that it is beyond the scope of the current review. We have added the following language regarding future directions in the end of section 6:
"Although systematically addressing the topic of offspring of parents with BD was beyond the scope of this article, it is important to note that there is also a need for large-scale RCTs examining the relative efficacy, tolerability, and safety of antidepressants vs. mood-stabilizers for anxiety and/or depression, and the efficacy, tolerability, and safety of stimulants for ADHD, among BD offspring."

Referee 2

This is a welcomed paper covering an area- paediatric bipolar disorder (PBD)- that has been tinged with controversy. As the authors contend, the area is in need of a fresh, authoritative review. In many senses this is a good article. However, there may be constraints on the length of the article, and, consequently, there is a danger of not fully addressing the previous problems. One of the mostly highly cited area has been the dispute over epidemiology, which have serious implications in the field, not least the introduction of the highly dubious diagnosis of DMDD in DSM 5. The citing of the meta–analysis (by one of the authors) (Van Meter, Moreira, & Youngstrom, 2011) which shows a roughly similar rate of BPI across countries is clear, but this study also shows, but not mentioned, higher rates of BP NOS in the US, and this needs comment. Indeed, epidemiological evidence of international hospital discharge rates show that BPI and other BP diagnoses are rare before puberty, except in the US. There is a danger that this issue of very early onset BP is not fully addressed, and studies -mostly US- that include very young subjects with BP NOS subjects become accepted as the norm in pharmacological and imaging studies.

How, for instance, is it possible for one recent large scale US TEAM study on the treatment of BPD with lithium, risperidone and sodium divalproex to have recruited more pre-pubertal subjects than adolescents with BPD (218 vs 61)(Geller et al., 2012)? This is a reasonable question, and it is not answered by asserting, as the paper does, that these issues are now been resolved.

RESPONSE: We agree with the point that pre-pubertal onset has had less research, particularly internationally, and remains both under-studied and a potential source of controversy and diagnostic ambiguity. The inconsistency and imprecision of reporting often worsens the situation. Fifteen of the seventeen epidemiological studies included cases with bipolar diagnoses other than BPI, but none reported rates of CYC separately, and few reported BP-NOS separately (or provided an operational definition of NOS). The apparently higher rate of NOS in the United States is confounded with reporting, where the Lewinsohn and NCS-A studies are two of the only that provided details about separate rates. Some of the specifics the reviewer mentions are examples of differences across studies that are difficult to interpret without more data points for comparison. We have not added detailed discussion of study specifics due to space constraints, but have added the following language, found in the second paragraph of the Conclusions: "Despite substantial increase in consensus regarding phenomenology and epidemiology, there remain outstanding questions about the prevalence of PBD in pre-pubertal children. Whereas the existence of PBD in pre-pubertal children has long been recognized, and indeed described in Kraepelin's seminal text(258), reliable and valid estimates of epidemiologic and clinical prevalence of PBD in pre-pubertal children are lacking. With the progress that has been made, in terms of parsing PBD from chronic irritability without episodic mania/hypomania, in terms of increased recognition of PBD, and in terms of screening and diagnostic instruments, the field is now better positioned to examine this topic than it was as recently as a decade ago."

The paper, correctly in my view, argues that the field has progressed and there is now more consensus. However, I would value the clarification on how many of the quoted papers rely on subjects with very early onset, that is below the age of 9. It may be contended, as the authors point out in the text, that a proportion of those with BP NOS go on to develop BP1-true, but not all, so how does this influence the field if those who do not progress to BP1 are included in the imaging and drug trials, or are we dealing with a largely unspecified group of BP type disorders?

RESPONSE: We agree. Frustratingly, the details are difficult to discern in the published literature. Of the 17 epidemiological studies, only four included children age 10 and younger (Pan et al., 2014 from Brazil, Stringaris et al., 2010, from the UK, Costello et al., 1996, from the USA, and Gould et al., 1998, from the USA), and none report the rates of BP separately for prepubertal or very young strata. There is concern that some of the interviews used might not be sensitive to bipolar disorder, and two of the studies predated research into bipolar NOS and did not systematically record it. The better data probably come from the prospective high risk studies, which support the view that rates

of incidence increase in adolescence. We agree that the current definitions also lump groups with heterogeneous courses together, and this adds noise to treatment and imaging work. We note this again in the Limitations to the treatment section: "Given concerns about heterogeneity of longitudinal course, it would be helpful to examine whether subtype of bipolar disorder or age of onset moderate treatment response."

The section on neuroimaging may be enhanced by more recent studies in diffusional imaging (DTI) which can add to the argument of altered ALC circuitry abnormalities

RESPONSE: We have updated the section on DTI with recent studies. Please see also our response to previous reviewer regarding expanding our fMRI and MRS section. In addition, the following language is now included in the neuroimaging section: "Diffusion tensor imaging (DTI) studies have investigated abnormalities in white matter microstructure of youth with PBD. Preliminary findings suggest the presence of abnormal white matter microstructure in superior frontal regions,(189, 190) and inferior/ventral frontal areas, such as orbitofrontal or anterior cingulate cortex, and anterior regions of the corpus callosum(191-195) compared to controls. One study found even greater reduction in white matter integrity in the anterior limb of the internal capsule in PBD versus adult BD.(196) Most of these studies have very small sample sizes, but together, they are consistent with a hypothesis of structural connectivity deficits between prefrontal-subcortical areas that underlie the prefrontal-limbic dysfunction in PBD."

Overall, despite criticisms, this is a good and, as stated at the beginning of the review, a needed paper at the right time. It would benefit from addressing the points outlined. It is titled an international task force, but it must be said the authors are mostly North American. There is nothing wrong with that, and the authors are acknowledged experts and they have, for example, addressed the unnecessary and damaging controversy concerning the over-reliance on chronic irritability as an important part of the diagnosis of PBD, which caused as much division within the US and outside the US. This paper may be sufficient on its own– it is broad ranging and does encompass a lot of the recent research on PBD, and it is neatly written and summarised- however, it does rely and cites mostly North American literature. A truly international approach may be a little more definitive.

RESPONSE: We appreciate the positive feedback, and we have incorporated additional international data as detailed below:

We have added Asian data about phenomenology, Chinese studies about imaging, and Asian studies about pharmacology, in addition to discussion of world data (five continents) in the epidemiology review and European as well as Canadian and US data about longitudinal course.

The section on neuroimaging may be enhanced by more recent studies in diffusional imaging (DTI) which can add to the argument of altered ALC circuitry abnormalities

RESPONSE: We agree (as does Reviewer 1), and we have added references to DTI studies (as detailed above).

Overall, despite criticisms, this is a good and, as stated at the beginning of the review, a needed paper at the right time. It would benefit from addressing the points outlined. It is titled an international task force, but it must be said the authors are mostly North American. There is nothing wrong with that, and the authors are acknowledged experts and they have, for example, addressed the unnecessary and damaging controversy concerning the overreliance on chronic irritability as an important part of the diagnosis of PBD, which caused as much division within the US and outside the US. This paper may be sufficient on its own– it is broad ranging and does encompass a lot of the recent research on PBD, and it is neatly written and summarised- however, it does rely and cites mostly North American literature. A truly international approach may be a little more definitive.

RESPONSE: We agree, and we sought to include international representation in the author team (Goldstein, Algorta, Zeni, Correll, Kim, Hillegers) as well as in the papers reviewed. We have added additional international studies as indicated above. We reviewed the reference list and count more than 70 articles that include international data, and we have added additional recent papers (e.g., Benarous et al., 2016). We are gratified by the growth of research interest in the topic internationally, and look forward to a time in the near future when an updated review will have the advantage of an even more globally diversified literature to review.