Expanded Topic Brief: Diagnosis of Bipolar Disorder in Children and Adolescents

Date: 12/18/2021
Nomination Number: 0961

Purpose: This document summarizes the information addressing a nomination submitted on November 19, 2021 through the Effective Health Care Website. This information was used 1) to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable (see Appendices); and 2) since the decision in this case was to not proceed with developing an evidence synthesis product, to provide more detailed information on the studies addressing the nomination that were found (presented as an expanded topic brief) in order to aid the nominator.

Issue: Since there are no diagnostic criteria specifically developed for bipolar disorder in children and adolescents, there is concern over the potential of overdiagnosis and overprescribing in youth. The nominators originally indicated that they would use a systematic review to either partner with a guideline group to develop diagnostic guidelines for bipolar disorder in youth or develop guidelines themselves to use in their healthcare system.

Findings: We found nine studies addressing the accuracy of methods for diagnosis of bipolar disorder in children and adolescents. To help inform the needs of the nominator on tools for diagnosis of bipolar disorder in youth, we have abstracted key information from these studies and provide this information in Tables 2a-2b.

Background

Bipolar disorder is a mental illness characterized by features such as unusual shifts in mood, energy, activity levels, and concentration.[1] Presentation may vary by age, with irritability being the dominant feature in childhood-onset, activity in adolescent-onset, and pressure of speech in adult-onset, bipolar disorder.[2] Onset typically occurs in late adolescence or early adulthood.[1] In children, the prevalence rate has been controversial and there is debate over how bipolar disorder may or may not present in prepubescent youth. Accurate diagnosis is critical due to the potential for over-diagnosis and subsequent over-prescribing of pharmacotherapy treatments that could introduce unnecessary harm.[3]

The 2020 NICE guidelines on bipolar disorder indicate that diagnosis and pharmacological treatment for children and adolescents largely follows guidelines for adults. In addition, they advise including the parents/caregivers and considering the young person's educational and social functioning when making a diagnosis.[4] The nominators are concerned that diagnosing bipolar disorder in children using criteria developed in adults may lead to overdiagnosis and overprescribing in children and would like diagnostic guidelines specifically tailored to youth.

Scope

1. What is the accuracy of methods for diagnosis of bipolar disorder in children and adolescents?

Contextual Question: What are best practices for diagnosis of bipolar disorder in children and adolescents?

Table 1. Questions and PICO (population, intervention, comparator, outcome)

Questions	1. Diagnosis of bipolar disorder in youth
Population	Children (5-12 yrs) and adolescents (13-18 yrs) with bipolar disorder; Comparator Populations: other diagnosed mental health conditions- anxiety, depression, family members, controls without mental health conditions
Interventions	Any assessment or other symptom evaluation
Comparators	Other assessment, clinical interview
Outcomes	Accuracy (e.g., sensitivity/specificity, positive predictive value), area under the curve, total scores or sub-scores (e.g., comparative assessment scores between individuals with bipolar and those with another mood disorder)

Expanded Topic Brief Methods

See Appendix A for information on the search strategies conducted for the assessment phase. For the development of the expanded topic brief, one reviewer assessed titles and abstracts from the entire literature yield from the search conducted in the assessment phase (November 22, 2016 – November 22, 2021). A second reviewer then assessed a random selection of 20% of the full yield of titles and abstracts, and the two reviewers came to a consensus on the inclusion/exclusion of studies in the sample. The primary reviewer then reviewed studies at full text for inclusion in the tables. The data presented in Tables 2a-2b was abstracted from the full texts and abstracts of the studies by one reviewer.

We did not assess study quality or evaluate the strength of evidence, and this expanded topic brief has not been externally peer reviewed. Its purpose is to assist the nominators as they assess how they can best provide quality care in their healthcare system.

Literature Findings

We found a limited number of primary studies with varied outcome measures. Specifically, from a review of the whole search yield, we found nine observational studies examining diagnostic assessment tools for bipolar disorder in youth (see Appendix A, Table 3). While three of these assessed the same tool, the Child Behavior Checklist,[5-7] the remainder of studies assessed various tools.[8-13] Table 2a is organized by the assessment tool(s) evaluated in the study and reports on participants' age, comparator populations and assessments, and study conclusions. Table 2b reports on the tools/methods used to diagnose bipolar disorder in the study participants.

Eight of the nine study designs were case control. One potential risk of this type of study design is the potential for confounding variables if there are systematic differences between the control and case groups other than the target exposure.

Table 2a. Characteristics and Main Conclusions of Included Studies from a Limited Search, November 22, 2016- November 22, 2021 (n=9)

Assessment Tool(s) Evaluated in the Study	Author, Year	Participant Age Mean (SD) Years	Comparator Population(s) Comparator Assessment(s), where applicable	Conclusions
CBCL-AAA	Cordeiro, 2020[1]	8.4 (1.3)-9.3 (1.3)	ADHD; PBD + ADHD; healthy controls	The CBCL-AAA-profile had good diagnostic prediction of PBD + ADHD.
CBCL-PBD	Cordeiro, 2020[1]	8.4 (1.3)-9.3 (1.3)	ADHD; PBD + ADHD; healthy controls	The CBCL-PBD can be used to screen for manic behavior and assist in differential diagnosis.
CBCL-BP	Yule, 2019[2]	11.7 (3.3)	ADHD; healthy controls	The CBCL-BP profile efficiently discriminated pediatric subjects with and without a structured interview diagnosis of BP-I disorder.
CBCL	Kweon, 2016[3]	14.9 (1.6)	Depressive disorder • P-GBI-10M • A-GBI (Adolescents completed) • A-MDQ (adolescents completed) • BDI (adolescents completed)	CBCL could be used for measuring mood symptoms and combined psychopathology, especially internalizing symptoms, in youth with mood disorder.
CBCL-DP	Kweon, 2016[3]	14.9 (1.6)	Depressive disorder • PGBI-10M • A-GBI (Adolescents completed) • A-MDQ (adolescents completed) • BDI (adolescents completed)	CBCL-DP had limited ability to differentiate bipolar from depressive disorder, at least in adolescents.

Assessment Tool(s) Evaluated in the Study	Author, Year	Participant Age Mean (SD) Years	Comparator Population(s) Comparator Assessment(s), where applicable	Conclusions
RIPoSt	Masi, 2021[4]	13.8 (2.3)	ADHD; ADHD + BSD; healthy controls CBCL	Affective instability and negative emotionality subscales, as well as negative emotional dysregulation, are higher in BSD, both pure and comorbid with ADHD, while emotional impulsivity is higher in the comorbid condition and similar in the ADHD and BSD alone group. The findings support the validity of the RIPoSt questionnaire, since the instrument proved to have good-to-excellent internal consistency, and strongly significant positive correlations were found with the CBCL-Dysregulation Profile, which is a commonly used, indirect measure of ED.
HAMD	Van Meter, 2021[5]	15.1 (1.5)	MDD; MDD+	Motor activity and hypersexuality items were consistently higher in BP than MDD groups. Subsyndromal manic symptoms during an episode of MDD offers the clearest way to differentiate bipolar from unipolar depression.
YMRS	Van Meter, 2021[5]	15.1 (1.5)	MDD; MDD+	Motor activity and hypersexuality items were consistently higher in BP than MDD groups. Subsyndromal manic symptoms during an episode of MDD offers the clearest way to differentiate bipolar from unipolar depression.
P- YMRS	Cordeiro, 2020[1]	8.4 (1.3)-9.3 (1.3)	ADHD; PBD + ADHD; healthy controls	PBD and PBD + ADHD were associated with similarly elevated P-YMRS scores. The P-YMRS can be used to screen for manic behavior and assist in differential diagnosis.
HCL-33	Zhang, 2021[6]	15.1 (1.4)	MDD	The HCL-33 seems to be a useful screening instrument to distinguish BD from depressed adolescents. However, considering certain less than robust psychometric properties, the HCL-33 needs to be modified and further refined for adolescent patients.
Machine learning algorithm using cognitive variables from the CANTAB	Bauer, 2019[7]	9.4 (3.2)-13.3 (3.0)	Unaffected offspring of BD parents, healthy controls	Findings suggest that alterations in affective processing and sustained attention are markers of BD in pediatric populations. Although cognitive measures may not have “diagnostic power” as such, clinicians may benefit from these preliminary findings to focus on the strongest predictors in borderline cases where diagnostic criteria may be unclear.

Assessment Tool(s) Evaluated in the Study	Author, Year	Participant Age Mean (SD) Years	Comparator Population(s) Comparator Assessment(s), where applicable	Conclusions
K-SADS- depression and mania items	Diler, 2017[8]	11.8 (2.0)-15.4 (3.7)	Unipolar depression	The results of this study suggest that it is possible to differentiate BP depression from unipolar depression based on depressive symptoms, and in particular subsyndromal manic symptoms.
CASI-4R	Ong, 2017[9]	9.3	Non-BPSD seeking outpatient mental health services PGBI-10M	Both the CASI-4R and the reference scale, PGBI-10M, distinguished BPSD from non-BPSD.

Abbreviations: AAA=Attention Problems, Aggressive Behavior, and Anxious/Depressed; ADHD=attention deficit hyperactivity disorder; A-GBI=76-item Adolescent General Behavior Inventory; A-MDQ=Adolescent-version of the Mood Disorder Questionnaire; BDI=Beck Depression Inventory; BP(-1)=bipolar disorder (-type 1); BSD/BPSD=bipolar spectrum disorders; CANTAB=Cambridge Neurocognitive Test Automated Battery; CASI-4R=Child and Adolescent Symptom Inventory-Revised, mania subscale; CBCL(-DP)=Child Behavior Checklist (-Dysregulation Profile); ED=emotional dysregulation; HAMD=Hamilton Depression Rating Scale; HCL-33=33-item Hypomania Checklist; K-SADS=Schedule for Affective Disorders and Schizophrenia for Children-Present Version; MDD(+)=major depressive disorder (+ mixed or psychotic features); PBD=pediatric-onset bipolar disorder; PGBI-10M=Parent General Behavior Inventory-10-item Mania; (P-)YMRS=(Parent-)Young Mania Rating Scale; RIPoSt=Reactivity, Intensity, Polarity and Stability.

Table 2b. Tools/Methods Used to Diagnose Bipolar Disorder

	Clinical interviews/ observations/ medical history	C-DISC	C-GAS	K-SADS-E	K-SADS-PL	DSM-IV	DSM-V	COBY	CBCL-6/18	ICD-10	HAMD	YMRS	CDRS	Family History-Research Diagnostic Criteria method	Family History Screen
Cordeiro, 2020[1]	✓	✓	✓												
Yule, 2019[2]	✓			✓											
Kweon, 2016[3]					✓	✓		✓							
Masi, 2021[4]	✓				✓		✓		✓						
Van Meter, 2021[5]	✓						✓								
Zhang, 2021[6]										✓	✓				
Bauer, 2019[7]	✓				✓							✓	✓		
Diler, 2017[8]				✓	✓									✓	✓
Ong, 2017[9]					✓										

Abbreviations: CBCL-6/18=Child Behavior Checklist for ages 6-18; C-DIS=Computerized Diagnostic Interview Schedule for Children; CDRS=Children Depression Rating Scale; C-GAS=Global Assessment Scale for Children; COBY=Course and Outcome of Bipolar Youth Study[10]; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); DSM-V=Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition); HAMD=Hamilton Depression Rating Scale; ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th Revision; K-SADS-E=Kiddie Schedule for Affective Disorders-Epidemiologic Version; K-SADS-PL=Kiddie Schedule for Affective Disorders- Present and Lifetime Versions; YMRS=Young Mania Rating Scale.

References

1. Bipolar Disorder. National Institute of Mental Health. doi: https://www.nimh.nih.gov/health/topics/bipolar-disorder.
2. Ryles F, Meyer TD, Adan-Manes J, et al. A systematic review of the frequency and severity of manic symptoms reported in studies that compare phenomenology across children, adolescents and adults with bipolar disorders. International journal of bipolar disorders. 2017;5(1):4-. doi: https://doi.org/10.1186/s40345-017-0071-y. PMID: 28155204.
3. Parry P, Allison S, Bastiampillai T. 'Pediatric Bipolar Disorder' rates are still lower than claimed: a re-examination of eight epidemiological surveys used by an updated meta-analysis. International Journal of Bipolar Disorders. 2021 2021/06/25;9(1):21. doi: https://doi.org/10.1186/s40345-021-00225-5.
4. Bipolar disorder: assessment and management. National Institute for Health and Care Excellence. doi: https://www.nice.org.uk/guidance/cg185.
5. Kweon K, Lee H-J, Park KJ, et al. Child behavior checklist profiles in adolescents with bipolar and depressive disorders. Comprehensive Psychiatry. 2016;70:152-8. doi: http://dx.doi.org/10.1016/j.comppsych.2016.07.007.
6. Yule A, Fitzgerald M, Wilens T, et al. Further Evidence of the Diagnostic Utility of the Child Behavior Checklist for Identifying Pediatric Bipolar I Disorder. Scandinavian Journal of Child & Adolescent Psychiatry & Psychology. 2019;7(1):29-36. doi: https://dx.doi.org/10.21307/sjcapp-2019-006. PMID: 32995342.
7. Cordeiro ML, Farias AC, Whybrow PC, et al. Receiver Operating Characteristic Curve Analysis of Screening Tools for Bipolar Disorder Comorbid With ADHD in Schoolchildren. Journal of Attention Disorders. 2020 08;24(10):1403-12. doi: https://dx.doi.org/10.1177/1087054715620897. PMID: 26721636.
8. Ong ML, Youngstrom EA, Chua JJ, et al. Comparing the CASI-4R and the PGBI-10 M for Differentiating Bipolar Spectrum Disorders from Other Outpatient Diagnoses in Youth. Journal of Abnormal Child Psychology. 2017 04;45(3):611-23. doi: https://dx.doi.org/10.1007/s10802-016-0182-4. PMID: 27364346.
9. Diler RS, Goldstein TR, Hafeman D, et al. Distinguishing Bipolar Depression from Unipolar Depression in Youth: Preliminary Findings. Journal of Child & Adolescent Psychopharmacology. 2017 May;27(4):310-9. doi: https://dx.doi.org/10.1089/cap.2016.0154. PMID: 28398819.
10. Masi G, Sesso G, Pfanner C, et al. An Exploratory Study of Emotional Dysregulation Dimensions in Youth With Attention Deficit Hyperactivity Disorder and/or Bipolar Spectrum Disorders. Frontiers in psychiatry Frontiers Research Foundation. 2021;12:619037. doi: https://dx.doi.org/10.3389/fpsyt.2021.619037. PMID: 33935827.
11. Van Meter A, Correll CU, Ahmad W, et al. Symptoms and Characteristics of Youth Hospitalized for Depression: Subthreshold Manic Symptoms Can Help Differentiate Bipolar from Unipolar Depression. Journal of Child & Adolescent Psychopharmacology. 2021 10;31(8):545-52. doi: https://dx.doi.org/10.1089/cap.2021.0057. PMID: 34637626.
12. Bauer IE, Suchting R, Van Rheenen TE, et al. The use of component-wise gradient boosting to assess the possible role of cognitive measures as markers of vulnerability to pediatric bipolar disorder. Cognitive Neuropsychiatry. 2019 03;24(2):93-107. doi: https://dx.doi.org/10.1080/13546805.2019.1580190. PMID: 30774035.

13. Zhang Y, Li W, Zhang WY, et al. Validation of the 33-item Hypomania Checklist (HCL-33) in screening adolescents with bipolar disorder. Journal of Affective Disorders. 2021 02 15;281:786-91. doi: https://dx.doi.org/10.1016/j.jad.2020.11.062. PMID: 33229023.
14. Berry EA, Heaton PT, Kelton CM. National estimates of the inpatient burden of pediatric bipolar disorder in the United States. J Ment Health Policy Econ. 2011 Sep;14(3):115-23. doi: https://pubmed.ncbi.nlm.nih.gov/22116169/. PMID: 22116169.

Author
Emily Gean
Lisa Winterbottom
Robin Paynter

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements
Christine Chang
Charlotte Armstrong

This report was developed by the Scientific Resource Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2017-00003C). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

Appendix A: Assessment Methods and Findings

Assessment Methods

We assessed the nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years, November 22, 2018-November 22, 2021, on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Joanna Briggs Institute http://joannabriggs.org/
- PsycINFO https://www.apa.org/pubs/databases/psycinfo
- Epistemonikos https://www.epistemonikos.org/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search for the last five years, November 2016- November 2021. We reviewed all studies identified titles and abstracts for inclusion. We estimated the size and scope of a potential evidence review.

Search strategy

Date searched: November 22, 2021
1*Bipolar Disorder/ or bipolar.ti,kf. (45258)
2exp *Diagnosis/ or di.fs. or ("bipolar index" or CBCL or CMRS or "child behavior checklist" or "child mania rating scale" or DSM-5 or "diagnostic and statistical manual").ti,ab,kf. or diagnos*.ti,kf. (5184347)
3and/1-2 (12956)
4limit 3 to "all child (0 to 18 years)" (3150)
5 3 and (*Pediatrics/ or (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* OR adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or school or school* or prematur* or preterm*).ti,ab,kf.) (1805)
6 or/4-5 (3519)
7 limit 6 to english language (3307)
8 7 not ((exp animals/ not humans/) or (animal model* or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or hamster* or horses or invertebrate or invertebrates or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or rodent* or sheep or simian or sow or sows or vertebrate or vertebrates or zebrafish).ti.) (3297)
9 8 not (comment or editorial or letter).pt. (3143)
10 randomized controlled trials as topic/ or comparative study/ or prospective studies/ (2525323)
11 ("randomized controlled trial" or "controlled clinical trial").pt. (640394)
12 (control* or group* or random* or trial).ti,ab. (7543441)
13 or/10-12 (9061879)
14 and/9,13 (1906)
15 limit 14 to yr="2018 - 2022" (267)
16 Meta-analysis/ or "Systematic Review"/ or (meta-anal* or metaanal* or ((evidence or systematic or scoping) adj3 (review or synthesis))).ti,ab. (407371)
17 and/9,16 (80)
18 limit 17 to yr="2018 - 2022" (29)
19 (((integrative or interpretive or "mixed method" or "mixed methods" or qualitative or realist or thematic) adj3 (synthes* or review*)) or ((framework or narrative) adj2 synthes*)).ti,ab,kf. (22158)
20 (mega-ethnograph* or megaethnograph* or meta-aggregat* or metaaggregat* or meta-ethnograph* or metaethnograph* or meta-interpret* or metainterpret* or meta-method* or metamethod* or meta-narrative* or metanarrative* or meta-study or metastudy or meta-synthe* or metasynthe* or meta-summary or metasummary or meta-triangulat* or metatriangulat*).ti,ab,kf. (2761)
21 ((qualitative adj2 (literature or paper or papers or research or study or studies)) and (synthes* or "systematic review" or "systematic reviews")).ti,ab,kf. (6490)
22 ((qualitative adj2 (literature or paper or papers or research or study or studies)) and ("literature search" or "literature searching" or "literature searches")).ti,ab,kf. (708)
23 ((qualitative adj2 (literature or paper or papers or research or study or studies)) and ("quality assessment" or "critical appraisal" or checklist*)).ti,ab,kf. (1896)
24 (((mixed or integrative) adj2 (method* or research or study or studies)) and (synthes* or "systematic review" or "systematic reviews")).ti,ab,kf. (4310)
25 (((mixed or integrative) adj2 (method* or research or study or studies)) and ("literature

search" or "literature searching" or "literature searches")).ti,ab,kf. (455)
26 (((mixed or integrative) adj2 (method* or research or study or studies)) and ("quality assessment" or "critical appraisal" or checklist*)).ti,ab,kf. (1109)
27 (CERQUAL or CONQUAL or JBI-QARI or QualSys or "Mixed Methods Appraisal Tool" or MMAT).ti,ab,kf. (950)
28 (Noblit and Hare).ab. (80)
29 or/19-28 (29413)
30 and/9,29 (7)
31 limit 30 to yr="2016 - 2022" (4)
32 exp Attitude/ or Focus Groups/ or Grounded Theory/ or "Interviews as Topic"/ or Narration/ or exp Qualitative Research/ or exp "Surveys and Questionnaires"/ or px.fs. (2337396)
33 ("critical interpretive" or "critical race" or "critical realism" or "critical realist" or emic or etic or ethnograph* or ethnolog* or hermeneutic* or heuristic* or "grounded theory" or phenomenolog* or semiotic*).ti,ab,kf,kw. (72809)
34 (((content or conversation or discourse or narrative or thematic) adj2 analy*) or ((cluster or purposive or theoretical) adj2 (sample* or sampling)) or "constant comparative" or descriptive or ethnonursing or ethno-nursing or (field adj1 (study or studies or work)) or fieldwork or "focus group" or "focus groups" or "key informant" or "key informants" or interview* or "mixed design" or "mixed methods" or qualitative or ((semi-structured or semistructured or unstructured or informal or in-depth or indepth or face-to-face or structured or guided) adj3 (discussion* or questionnaire*)) or survey* or thematic or triangulat*).ti,ab,kf,kw. (1423927)
35 (attitud* or barrier* or benefit* or context* or emotion* or facilitator* or experienc* or narratives or opinion* or perception* or perspective* or preference* or react* or theme or themes or value* or valuing or viewpoint* or view or views).ti,ab. (7226432)
36 or/32-35 (9097632)
37 and/9,36 (2381)
38 limit 37 to yr="2016 - 2022" (479)
39 exp case-control studies/ or exp cohort studies/ or epidemiologic methods/ or (cohort* or (case$1 and control$1)).tw. (3081834)
40 and/9,39 (1019)
41 limit 40 to yr="2016 - 2022" (273)

Cochrane Central Register of Controlled Trials (Ovid EBM Reviews)
Date search: November 22, 2021
1 Bipolar Disorder/ or bipolar.ti. (6309)
2 Diagnosis/ or ("bipolar index" or CBCL or CMRS or "child behavior checklist" or "child mania rating scale" or DSM-5 or "diagnostic and statistical manual").ti,ab. or diagnos*.ti. (24225)
3 and/1-2 (236)
4 3 and (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* OR adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or school or school* or prematur* or preterm*).ti,ab. (56)
5 limit 4 to yr="2016 - 2022" (28)

PsycINFO (Ovid)
Date searched: November 22, 2021
1 Bipolar Disorder/ or Bipolar I Disorder/ or Bipolar II Disorder/ or bipolar.ti. (29757)
2 Diagnosis/ or Differential Diagnosis/ or ("bipolar index" or CBCL or CMRS or "child behavior

checklist" or "child mania rating scale" or DSM-5 or "diagnostic and statistical manual").ti,ab. or diagnos*.ti. (111837)
3 and/1-2 (3058)
4 limit 3 to ((childhood <birth to 12 years> or adolescence <13 to 17 years>) and (100 childhood <birth to age 12 yrs> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)) (662)
5 3 and (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* OR adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or school or school* or prematur* or preterm*).ti,ab. (780)
6 or/4-5 (931)
7 limit 6 to english language (870)
8 limit 7 to yr="2018 - 2022" (97)
9 8 and (meta-anal* or metaanal* or ((evidence or systematic or scoping) adj3 (review or synthesis))).ti,ab. (5)
10 limit 8 to 1300 metasynthesis (0)
11 limit 7 to yr="2016 - 2022" (150)
12 11 and (control* or group* or random* or trial).ti,ab. (75)
13 limit 11 to ("0700 interview" or "0750 focus group" or 1600 qualitative study) (21)
14 11 and (cohort* or (case$1 and control$1)).ti,ab. (20)

Clinical Trials.gov

Assessment Findings

Table 3. Literature identified for each Question

Question	Systematic reviews (11/2018-11/2021)	Primary studies (11/2016-11/2021)
Question 1: Diagnosis of bipolar disorder in youth	Total: 0	Total: 9 • RCT: 0 • Case control: 8 • Cross-sectional: 1 Clinicaltrials.gov • Recruiting: 0

Summary of Selection Criteria Assessment

There are currently no diagnostic criteria specifically for children and adolescents with bipolar disorder. Having such criteria may be particularly important given a history of controversy regarding the prevalence of childhood-onset bipolar disorder, and, consequentially, concern about overdiagnosis and overprescribing. Based on our review of the literature, however, current evidence is sparse. The EPC program will not develop a new evidence synthesis product due to the nature of the literature findings.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	An estimated 2.9% of adolescents in the U.S. have bipolar disorder.[1] The prevalence in children is debated.[3]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Children and adolescents represent a vulnerable population.
2c. Incorporates issues around both clinical benefits and potential clinical harms	No
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. In 2006 in the U.S., the total cost of pediatric bipolar disorder was USD 233 million.[14]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	No. There were no existing systematic reviews found addressing the key question.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. Existing guidelines reference adult-derived criteria for diagnosis of bipolar disorder in children and adolescents and no youth-specific guidelines exist.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. There is a history of controversy over the prevalence of childhood-onset bipolar disorder due to debate over the diagnosis of the condition in pre-pubescent youth.[3]
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	*Size/scope of review:* Nine studies from a review of the entire yield. The estimated size of a new review would be limited. *ClinicalTrials.gov*.: none

Abbreviations: AHRQ=Agency for Healthcare Research and Quality;