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 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.

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 would like 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: The EPC Program will not develop a new systematic review because we did not find enough primary studies addressing the concerns of this nomination.

Background

Bipolar disorder is a mental illness characterized by features such as unusual shifts in mood, energy, activity levels, and concentration. 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. Onset typically occurs in late adolescence or early adulthood. 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.

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. 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)

<table>
<thead>
<tr>
<th>Questions</th>
<th>1. Diagnosis of bipolar disorder in youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>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</td>
</tr>
<tr>
<td>Interventions</td>
<td>Any assessment or other symptom evaluation</td>
</tr>
<tr>
<td>Comparators</td>
<td>Other assessment, clinical interview</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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)</td>
</tr>
</tbody>
</table>

Assessment Methods
See Appendix A.

Summary of 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. While three of these assessed the same tool, the Child Behavior Checklist, the remainder of studies assessed various tools.

Table 2. Literature identified for each Question

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Question 1: Diagnosis of bipolar disorder in youth</td>
<td>Total: 0</td>
<td>Total: 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RCT: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Case control: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cross-sectional: 1</td>
</tr>
<tr>
<td></td>
<td>Clinicaltrials.gov</td>
<td>Recruiting: 0</td>
</tr>
</tbody>
</table>

See Appendix B for detailed assessments of all EPC selection criteria.

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.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.
References
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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements
Charlotte Armstrong

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Appendix A: 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
  - EHC Program [https://effectivehealthcare.ahrq.gov/](https://effectivehealthcare.ahrq.gov/)
  - AHRQ Technology Assessment Program [https://www.ahrq.gov/research/findings/ta/index.html](https://www.ahrq.gov/research/findings/ta/index.html)
- US Department of Veterans Affairs Products publications
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program [https://www.healthquality.va.gov/](https://www.healthquality.va.gov/)
- Cochrane Systematic Reviews [https://www.cochranelibrary.com/](https://www.cochranelibrary.com/)
- University of York Centre for Reviews and Dissemination database [https://www.crd.york.ac.uk/CRDWeb/](https://www.crd.york.ac.uk/CRDWeb/)
- PROSPERO Database (international prospective register of systematic reviews and protocols) [http://www.crd.york.ac.uk/prospERO/](http://www.crd.york.ac.uk/prospERO/)
- Epistemonikos [https://www.epistemonikos.org/](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 2018- 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 syntheses*).ti,ab,kf. (22158)
20 (mega-ethnograph* or megaethnograph* or meta-aggregat* or metaaggregat* or metaethnograph* 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")) or (literature search" or "literature searching" or "literature searches").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 experience* 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 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
### Appendix B. Selection Criteria Assessment

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Assessment</th>
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</thead>
<tbody>
<tr>
<td>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.?</td>
<td>Yes</td>
</tr>
<tr>
<td>1b. Is the nomination a request for an evidence report?</td>
<td>Yes</td>
</tr>
<tr>
<td>1c. Is the focus on effectiveness or comparative effectiveness?</td>
<td>Yes</td>
</tr>
<tr>
<td>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?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Importance</td>
<td></td>
</tr>
<tr>
<td>2a. Represents a significant disease burden; large proportion of the population</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Yes. Children and adolescents represent a vulnerable population.</td>
</tr>
<tr>
<td>2c. Incorporates issues around both clinical benefits and potential clinical harms</td>
<td>No</td>
</tr>
<tr>
<td>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</td>
<td>Yes. In 2006 in the U.S., the total cost of pediatric bipolar disorder was USD 233 million.</td>
</tr>
<tr>
<td>3. Desirability of a New Evidence Review/Absence of Duplication</td>
<td></td>
</tr>
<tr>
<td>3. A recent high-quality systematic review or other evidence review is not available on this topic</td>
<td>No. There were no existing systematic reviews found addressing the key question.</td>
</tr>
<tr>
<td>4. Impact of a New Evidence Review</td>
<td></td>
</tr>
<tr>
<td>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)?</td>
<td>Yes. Existing guidelines reference adult-derived criteria for diagnosis of bipolar disorder in children and adolescents and no youth-specific guidelines exist.</td>
</tr>
<tr>
<td>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</td>
<td>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.</td>
</tr>
<tr>
<td>5. Primary Research</td>
<td></td>
</tr>
<tr>
<td>5. Effectively utilizes existing research and knowledge by considering:</td>
<td></td>
</tr>
<tr>
<td>- Adequacy (type and volume) of research for conducting a systematic review</td>
<td>Size/scope of review: Nine studies from a review of the entire yield. The estimated size of a new review would be limited.</td>
</tr>
<tr>
<td>- Newly available evidence (particularly for updates or new technologies)</td>
<td>ClinicalTrials.gov.: none</td>
</tr>
</tbody>
</table>

**Abbreviations:** AHRQ=Agency for Healthcare Research and Quality;