

Prioritization of Research Addressing Antipsychotics for Adolescents and Young Adults With Bipolar Disorder

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Despite a paucity of high-quality evidence about benefits and harms, antipsychotic medication use among adolescents and young adults with bipolar disorder is increasing. The Patient-Centered Outcomes Research Institute tasked the Duke Evidence Synthesis Group with creating a prioritized agenda for research in this area that would incorporate the perspectives of relevant stakeholders. We identified a list of potential evidence gaps by reviewing existing literature and engaged a diverse group of 9 stakeholders to expand and refine this list. Using a forced-ranking prioritization method, stakeholders prioritized 10 of 23 potential evidence gaps as the

most pressing for future research. These evidence gaps relate to 3 areas: the comparative effectiveness of intervention strategies, the effect of antipsychotics on patient-centered outcomes, and the influence of various patient characteristics on antipsychotic effectiveness. In addition to presenting these findings, we suggest appropriate study designs for addressing the stakeholder-prioritized research questions.

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Bipolar disorder is characterized by episodes of mania (mood elevation, delusions, and extreme behaviors) alternating with severe depressive symptoms. It may develop during childhood or adolescence, and symptoms seem to be more severe when onset occurs at a young age (1, 2). Adolescents and young adults (aged <25 years) with bipolar disorder have high rates of substance abuse, hospitalization, legal issues, academic and psychosocial functional impairment, and suicide. These outcomes may occur more frequently when bipolar disorder coexists with other psychiatric disorders, low socioeconomic status, or abuse. The disorder also affects relationships and the financial security of the families.

Up to 2.7% of persons aged 12 to 21 years have bipolar disorder, although rates may approach 5% when those with subsyndromal manic symptoms, who are also at elevated risk for morbidity, are included in estimates (3). Diagnosing the disorder in adolescents and young adults is complex and requires longitudinal assessment. Bipolar disorder may be difficult to distinguish from other disorders affecting adolescents and young adults, such as attention-deficit hyperactivity disorder and behavioral disorders, and diagnosis is further complicated by the fact that bipolar disorder may coexist with these other disorders. Psychiatric interviews and rating scales can be used for screening by trained clinicians, and parent-report instruments have also been used (4–6).

Recovery is achievable in most adolescents and young adults with bipolar disorder (7–10), but almost 80% of the affected population relapse within 2 to 5 years (9). Options for treating the disorder include medications (for example, antipsychotic drugs, lithium, and certain antiepileptic drugs), behavioral therapy interventions, and peer support. A lack of high-quality longitudinal studies comparing the effectiveness of different therapeutic options in adolescents and young adults complicates treatment of this population.

The use of antipsychotic agents to treat bipolar disorder in adolescents and young adults has increased significantly during the past 20 years (11). Several factors have contributed to this occurrence. First, high-quality randomized, placebo-controlled trials have shown that second-generation antipsychotics are effective antimanic agents (12). On the basis of these data, aripiprazole, olanzapine, risperidone, and quetiapine have received regulatory approval for pediatric bipolar mania. Second, head-to-head trials have shown second-generation antipsychotics to be superior to valproic acid and lithium for treating mania in children and adolescents (13–15). Finally, recent promotion by the pharmaceutical industry spurred by new indications for pediatric bipolar disorder has increased use of second-generation antipsychotics.

However, use of antipsychotics in adolescents and young adults remains controversial because of the paucity of population-specific data on which to base practice recommendations (16) and existing concern that bipolar disorder diagnosis may be applied too broadly, including for patients with chronic mood dysregulation (17). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, includes a new diagnosis—disruptive mood dysregulation disorder—to reduce premature bipolar disorder assignment, but concerns about the validity of this new diagnosis have been raised (18, 19). Antipsychotic medications may also produce significant adverse effects (16, 20). First-generation antipsychotics can cause extrapyramidal

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symptoms, dry mouth, sedation, and the neuroleptic malignant syndrome, whereas second-generation antipsychotics can cause weight gain, diabetes, dyslipidemia, and hyperprolactinemia.

Because antipsychotic use among adolescents and young adults with bipolar disorder is increasing despite significant clinical uncertainty, further research exploring the comparative effectiveness of antipsychotics on patient-centered outcomes in these populations is needed. Using a process described on the Patient-Centered Outcomes Research Institute (PCORI) Web site and in our companion paper (21), a PCORI advisory panel has identified this topic as being of high interest for potential targeted funding. Accordingly, PCORI tasked the Duke Evidence Synthesis Group with creating a prioritized agenda for research in this area that would incorporate the perspectives of relevant stakeholders.

METHODS

The **Appendix Figure** (available at www.annals.org) and the companion paper (21) detail the methods used to prioritize future research and develop recommendations. We surveyed existing literature with a focus on systematic reviews (2008 to 2013), particularly an Agency for Healthcare Research and Quality report identifying future research needs for antipsychotic use in children and young adults with various psychiatric conditions (22, 23). On the basis of recommended areas for future research from these sources, we developed a draft list of 21 possible evidence gaps (**Table 1** of the **Supplement**, available at www.annals.org).

We then engaged a group of 9 stakeholders, which included clinical experts and researchers in bipolar disorder, representatives from federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision makers and policymakers, and representatives from related consumer and patient advocacy groups (**Table 2** of the **Supplement**). In each of these categories, we identified a person with clinical or methodological expertise. We received feedback on potential stakeholders from the Research Triangle Institute-University of North Carolina Evidence-based Practice Center, which wrote the aforementioned future research needs report on antipsychotic use in children and young adults (23), and from PCORI's patient engagement group. Potential stakeholders completed a statement of disclosure and were screened for conflicts of interest.

We sought input from these stakeholders on our draft list of possible evidence gaps, and we modified certain gaps and added others on the basis of their feedback, which led to a finalized list. From this list, we constructed an analytic framework (**Figure**) by adapting a previously used framework and incorporating the stakeholder-refined list of possible evidence gaps (23). By using a forced-ranking prioritization method (24), stakeholders then prioritized the list

of possible evidence gaps through Web-based surveys. We used this input to rank the finalized list of possible evidence gaps into 3 tiers of priority.

For topics related to the 10 highest-priority ("top-tier") evidence gaps, we did a horizon scan for recent and ongoing studies by searching PubMed and ClinicalTrials.gov (2008 to 2013) for projects that presented original data or secondary analysis of data from a randomized, controlled trial (RCT), prospective or retrospective observational study, or registry; included data on first- and second-generation antipsychotic medications; included adolescents or young adults with bipolar disorder; and included outcomes that could be categorized according to the identified list of research priorities. Our search strategy is presented in **Table 3** of the **Supplement**. We then determined the most appropriate study designs for the 10 stakeholder-ranked research areas of highest priority.

Role of the Funding Source

Funding for this work was provided by PCORI. The funding source stipulated the topic for prioritization but did not participate in the literature search, determination of study eligibility criteria, data analysis or interpretation, or preparation and approval of the manuscript for publication. The funding source did review a draft version of the manuscript and provided suggestions to clarify language describing the process in selecting this topic for prioritization.

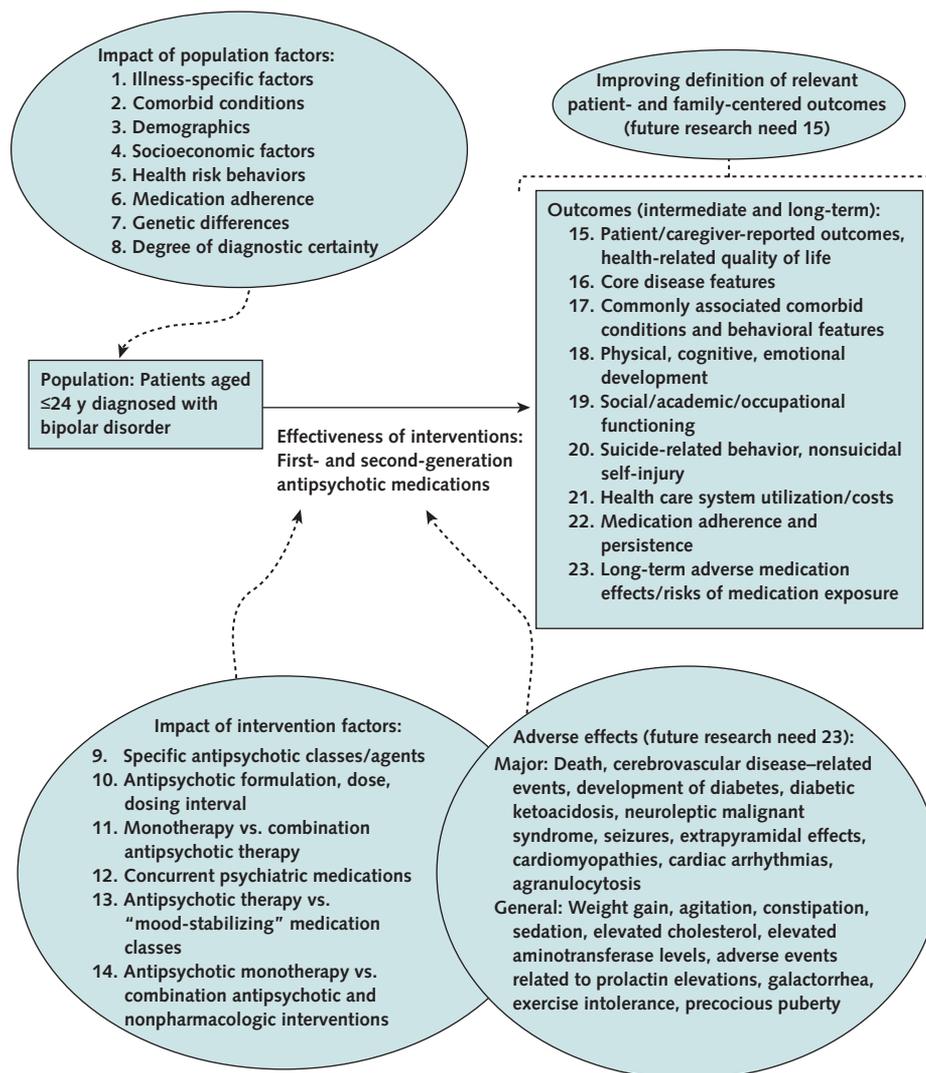
RESULTS

Expansion of Evidence Gaps Through Stakeholder Engagement

All 9 invited stakeholders participated in teleconferences to refine and expand the initial list of 21 evidence gaps (**Table 1** of the **Supplement**). Three themes emerged during these discussions, which informed our expansion of the list. First, stakeholders highlighted how uncertainty in distinguishing bipolar disorder from attention-deficit hyperactivity disorder and other behavioral disorders can complicate diagnosis and interpretation of existing research in younger patients. This uncertainty often necessitates treatment in the absence of a firm diagnosis, which may confound outcome ascertainment. In addition to diagnostic uncertainty, stakeholders pointed to uncertainty in how phase and severity of illness are best measured and how these factors affect treatment choices.

Second, our stakeholders discussed how our focus on adolescents and young adults requires consideration of a broad set of patient-centered outcomes in potential studies. These include outcomes measured over long periods; developmental outcomes; functional status outcomes; outcomes relating to parents, caregivers, or family members, including economic outcomes; and outcomes related to offspring in women of childbearing age (such as pregnancy, neonatal, and childhood outcomes).

Figure. Analytic framework.



Finally, although the specific clinical domain addressed by this project focused on antipsychotic drug therapy, our stakeholders emphasized that the efficacy of such therapy for bipolar disorder in adolescents and young adults compared with alternative drug classes remains uncertain for many subgroups of patients. As such, stakeholders believed that attention needed to be given to research comparing antipsychotics with alternative treatment strategies, including lithium, antiepileptic drugs, and adjunctive nonpharmacologic treatments (such as therapy interventions and peer support).

Stakeholder Ranking of Future Research Needs

The Appendix Table (available at www.annals.org) shows the 23 final potential research topics, the number of points each received, and the number of stakeholders who allotted points to each topic. The final ranking divides the

possible evidence gaps into top, middle, and lower tiers based on the overall score. Of note, several gaps received a score of 4, including 3 at the bottom of the top tier and 4 at the top of the middle tier. We included gaps ranked 3 and 4 in our top tier because 2 stakeholders noted during the prioritization exercise that they believed these 2 questions were similar enough to be combined. If they had been combined, this inclusive gap would have received a score of 8, with prioritization from 4 stakeholders. We included gap 16 in the top tier because, unlike the other gaps receiving a score of 4, it was assigned priority by 4 stakeholders rather than 3.

The top tier therefore comprised the following 10 evidence gaps (in descending order of priority): effectiveness of monotherapy with antipsychotics versus combination therapy with "mood-stabilizing" medications; effect of an-

tipsychotics on social, academic, and occupational functioning; defining key patient- and family-centered outcomes; effectiveness of psychiatric medications other than those from the mood-stabilizing class given as adjuncts to antipsychotics; effectiveness of mood-stabilizing medications versus antipsychotics; effectiveness of antipsychotics alone versus in combination with nonpharmacologic interventions; adverse effects of short- and long-term antipsychotic exposure; effect of demographic differences on the effectiveness of antipsychotics; effect of socioeconomic factors on the effectiveness of antipsychotics; and effect of antipsychotics on core disease features immediately and in the long term.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

Our PubMed search identified 1563 articles. Of these, 42 met our inclusion criteria, including 6 systematic reviews, 20 RCTs, 15 cohort studies, and 1 case-control study. Sample sizes ranged from 16 to 296 patients for RCTs and from 12 to 8129 patients for cohort studies, and the case-control study involved 40 patients. Three studies focused only on young adults, 3 focused on adolescents and young adults, and the remainder (85.7%) targeted adolescents or older children. Seventeen studies (40.5%) were active comparator studies, 13 (31.0%) were placebo-controlled or used the standard of care as the comparison, and 12 (28.6%) had no comparator. No recently published

studies were found that pertained to one of the prioritized research areas (effect of socioeconomic factors on antipsychotic effectiveness).

Our search of ClinicalTrials.gov identified 95 protocols submitted since 1 January 1998. Of these, we identified 42 as potentially relevant to the top-tier research questions: 2 were open and enrolling, 7 were active and not enrolling, 1 was enrolling by invitation only, and 32 had been recently completed. These protocols included 30 RCTs, 1 observational study, and 11 nonrandomized interventional trials. Sample sizes ranged from 13 to 5000 patients. For 2 of the prioritized research questions (effect of antipsychotics on social, academic, and occupational functioning and effect of socioeconomic factors on antipsychotic effectiveness), we identified no ongoing studies.

Tables 4 through 12 of the Supplement summarize key characteristics of the included PubMed and Clinical Trials.gov articles separately for each of the 10 top-tier future research needs. Of note, the completed studies did not lessen the stakeholder panel's enthusiasm for needed research in these areas.

Suggested Research Design Considerations

The Table summarizes our suggestions for appropriate study designs to address the 10 top-tier research priorities. Table 13 of the Supplement provides additional details

Table. Study Designs Suggested for Top-Tier Future Research Needs for Management Strategies for Bipolar Disorder

Rank	Prioritized Future Research Need	Recommended Study Design
1	What are the comparative safety and effectiveness of antipsychotic monotherapy compared with combination therapy with medications from the "mood-stabilizing" class in adolescents/young adults with bipolar disorder?	RCT or observational study using existing data
2	What are the comparative effects of antipsychotics on social, academic, and occupational functioning in adolescents/young adults with bipolar disorder?	RCT or observational study involving new data collection
3	What are the key patient- and family-centered outcomes for adolescents/young adults with bipolar disorder and their families, and how are these outcomes affected by different antipsychotic classes/agents?	Observational study involving new data collection
4	What are the comparative safety and effectiveness of concurrent psychiatric medications not belonging to the "mood-stabilizing" class given as adjuncts to antipsychotic drugs in adolescents/young adults with bipolar disorder?	RCT or observational study using existing data
5	What are the comparative safety and effectiveness of "mood-stabilizing" medication classes compared with antipsychotic drugs in adolescents/young adults with bipolar disorder?	RCT or observational study using existing data
6	What are the comparative safety and effectiveness of antipsychotic drugs alone compared with the combination of antipsychotic drugs plus other nonpharmacologic interventions in adolescents/young adults with bipolar disorder?	RCT or observational study involving existing or new data collection
7	What are the adverse effects of short- and long-term medication exposure between and within antipsychotic classes for adolescents/young adults with bipolar disorder, and how do these adverse effects vary on the basis of patient characteristics?	RCT or observational study involving existing or new data collection
8	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on demographic differences?	Meta-analysis of observational studies or observational study involving existing or new data collection
9	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on socioeconomic factors?	Meta-analysis of observational studies or observational study involving existing or new data collection
10	What are the comparative effects of antipsychotics on core disease features in adolescents/young adults with bipolar disorder, both immediately and in the long term?	RCT, meta-analysis, or individual-patient data analysis of existing RCTs, or observational study using existing data

RCT = randomized, controlled trial.

about possible advantages and disadvantages of multiple study designs for each prioritized evidence gap.

DISCUSSION

Bipolar disorder incidence and prevalence are increasing among adolescents and young adults (25, 26), and access to evidence-based treatment options is essential. Antipsychotic medication use in these populations has increased (11), but the evidence supporting the effectiveness and safety of these medications compared with other available treatment options has not kept pace. Challenges in diagnosing adolescents and young adults with bipolar disorder in clinical practice have further complicated the management of this condition (18, 19). In order for patients, providers, and other stakeholders to make informed decisions about the treatment of bipolar disorder in these age groups, new patient-centered research is needed.

Previous reviews have evaluated gaps in the evidence base supporting the use of first- and second-generation antipsychotics for children and young adults. Although not specific to bipolar disorder, a 2012 project sponsored by the Agency for Healthcare Research and Quality (23) identified key areas in which further research exploring antipsychotic use in younger populations was indicated. These included the long-term effectiveness of antipsychotic medications in children and young adults, which is measured in outcomes of interest; long-term risks of antipsychotic medication exposure in those age groups; and subgroups of patients in whom antipsychotic medications differ in efficacy, effectiveness, or frequency of adverse events. Our stakeholders' input echoes these themes and builds on them by identifying concrete areas in which funding to support future research would most enhance the evidence base on the use of antipsychotic medications in children and young adults.

Of the 23 potential research needs considered in this project, the top tier comprises 10 questions that can be organized into 3 areas. First, several research needs relate to specific interventions for adolescents and young adults with bipolar disorder. These include the comparative safety and effectiveness of monotherapy with antipsychotics compared with combination therapy with mood-stabilizing medications, concurrent psychiatric medications other than mood stabilizers given as adjuncts to antipsychotics, mood-stabilizing medications compared with antipsychotics, and antipsychotic drugs alone versus in combination with nonpharmacologic interventions. These needs point to uncertainty about the use of specific intervention strategies for bipolar disorder among adolescents and young adults and suggest that future research in these areas would enhance patient-centered care for this vulnerable population. As evidenced by the summary of existing and ongoing studies, research addressing these evidence gaps is ongoing but additional comparative studies evaluating the effect

of diverse treatment regimens on short- and long-term patient-centered outcomes are needed to adequately inform care.

Second, several research needs concerned specific outcomes of interest for antipsychotic medication use in adolescents and young adults with bipolar disorder. These include the comparative effects of antipsychotics on social, academic, and occupational functioning; defining the key patient- and family-centered outcomes for antipsychotic medication use; short- and long-term adverse effects of antipsychotic medication exposure; and the comparative effects of antipsychotics on core disease features immediately and in the long term. These needs point to uncertainty about appropriate metrics for antipsychotic use among adolescents and young adults with bipolar disorder and how antipsychotic medications affect these metrics. Although several studies are exploring these outcomes of interest, studies assessing longer-term outcomes and adverse effects across available treatments remain scarce.

Finally, 2 research needs relate to how patient factors may affect the use of antipsychotic medications in adolescents and young adults with bipolar disorder. These include variation in antipsychotic medication safety and effectiveness depending on demographic differences and socioeconomic factors. These research needs point to uncertainty about how patient factors modulate the effect of antipsychotic medications in adolescents and young adults and suggest that future research in these areas would enhance patient-centered care for this population.

The Duke Evidence Synthesis Group was tasked with evaluating future research needs pertaining to the use of antipsychotic medications in adolescents and young adults with bipolar disorder, and the list of evidence gaps was compiled with this objective in mind. However, the prioritized list may not reflect the full range of possible future research needs relating to bipolar disorder in this population. For example, although we included a future research need relating to the effect of diagnostic uncertainty on therapeutic choices and the effectiveness and safety of antipsychotics in adolescents and young adults, a full exploration of the topic of diagnostic uncertainty was beyond the scope of this project. In addition, our group of stakeholders was relatively small, and another group might rank the identified future research needs differently. Furthermore, because a comprehensive systematic review has not been done for many of the identified evidence gaps, we cannot determine with certainty the degree to which prioritized future research needs have already been addressed. Finally, our study design recommendations consider only methodological issues. We recognize that real-world factors, such as the feasibility of conducting RCTs in young adult populations, may also affect the selection of study designs to further evaluate these gaps.

Treatment of bipolar disorder with antipsychotic medications among adolescents and young adults is increasing, but the evidence base supporting the patient-centered com-

parative effectiveness and safety of these medications has not kept pace. In order for patients, providers, and other stakeholders to make informed decisions, new patient-centered research is needed. On the basis of input from our stakeholder group, key research priorities pertaining to antipsychotic use in adolescents and young adults with bipolar disorder include the comparative effectiveness of treatment strategies, the effect of antipsychotics on specific outcomes, and the effect of patient characteristics on antipsychotic effectiveness. We hope that future research stimulated by this prioritized agenda will help address the identified gaps and improve patient outcomes.

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Dream of a Suicide

What does it mean?

That I dreamed you
tall and whole.

Strong, straight and well,
with a practiced patter:
sharp as a cutting remark.

You would think it was funny, too,
that you were gay in my dream.
Completely, limp-wristedly,
a flamingo in style,
violently fashionable.

You wore a silver jumpsuit,
like a mirrored disco ball,
and had a bowl haircut,
(What were you thinking?)
and grinned like a shark.

What does it mean?

That I dreamed you a future,
and it was FABulous.

Did I dream you an afterlife?
A beauty school dropout, frankie avalon heaven?

Maybe it means I forgive you,
But I'm sure it means I still love you,
funny little brother,
And oh, how I hope,
the pearlygate smile and gossip benediction awaits us all.

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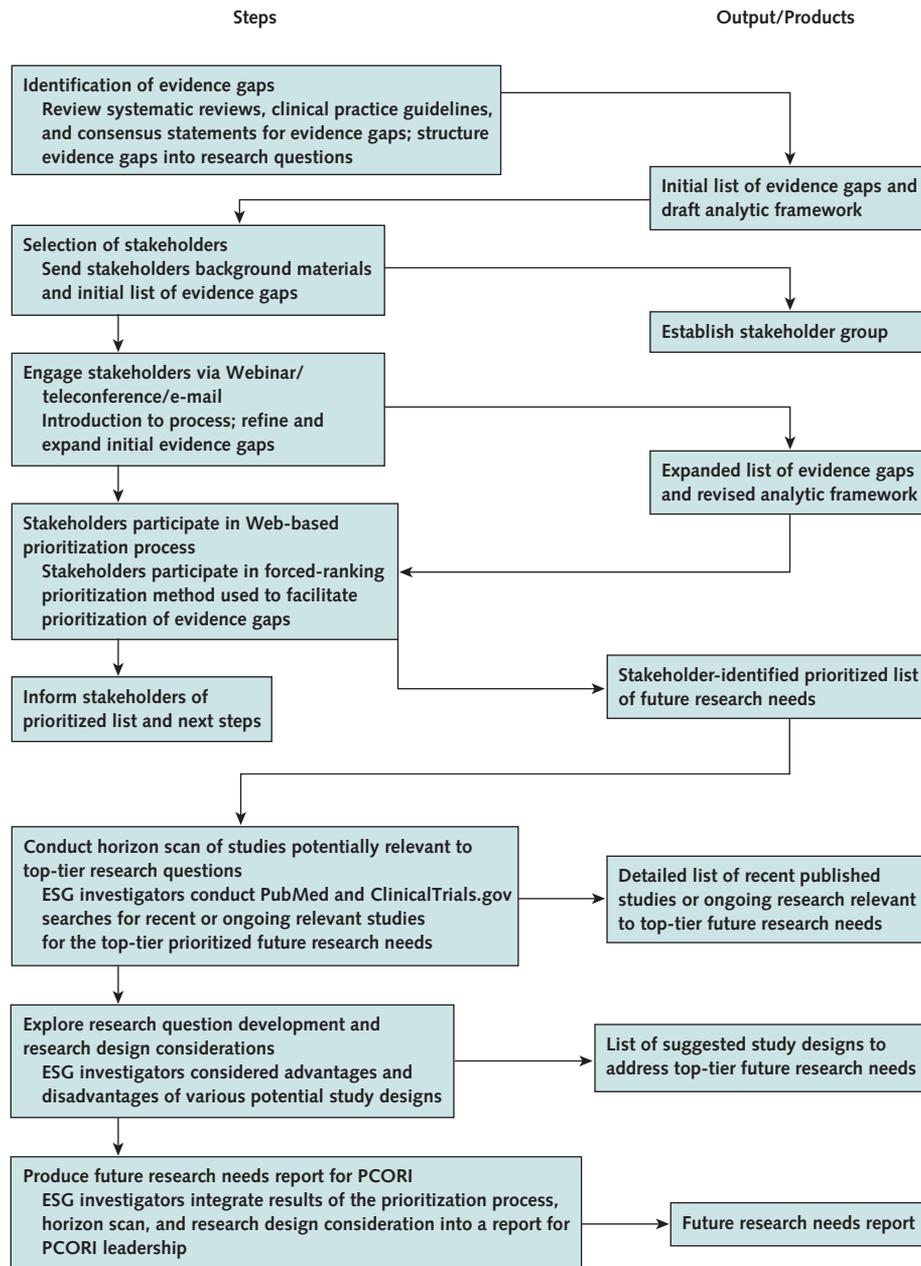
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Appendix Figure. Overview of prioritization process.



Adapted from reference 27. ESG = Evidence Synthesis Group; PCORI = Patient-Centered Outcomes Research Institute.

Appendix Table. Final Ranking of Future Research Needs for Management Strategies for Bipolar Disorder*

Rank	Question	Score	Stakeholders, <i>n</i>
Top tier			
11	What are the comparative safety and effectiveness of antipsychotic monotherapy compared with combination therapy with medications from the "mood-stabilizing" class in adolescents/young adults with bipolar disorder?	12	6
19	What are the comparative effects of antipsychotics on social, academic, and occupational functioning in adolescents/young adults with bipolar disorder?	9	6
15	What are the key patient- and family-centered outcomes for adolescents/young adults with bipolar disorder and their families, and how are these outcomes affected by different antipsychotic classes/agents?	8	5
12	What are the comparative safety and effectiveness of concurrent psychiatric medications not belonging to the "mood-stabilizing" class given as adjuncts to antipsychotic drugs in adolescents/young adults with bipolar disorder?	7	5
13	What are the comparative safety and effectiveness of "mood-stabilizing" medication classes (e.g., lithium or antiepileptic drugs, such as lamotrigine or valproic acid) compared with antipsychotic drugs in adolescents/young adults with bipolar disorder?	7	5
14	What are the comparative safety and effectiveness of antipsychotic drugs alone compared with the combination of antipsychotic drugs plus other nonpharmacologic interventions (e.g., psychotherapy/counseling, peer and family support, supported employment, diet and physical activity interventions, or assertive community treatment) in adolescents/young adults with bipolar disorder?	6	4
23	What are the adverse effects of short- and long-term medication exposure between and within antipsychotic classes for adolescents/young adults with bipolar disorder, and how do these adverse effects vary on the basis of patient characteristics?	5	5
3†	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on demographic differences, such as age group (e.g., >18 y vs. 18–25 y), rural versus urban dwelling, race/ethnicity, or sex?	4	3
4†	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on socioeconomic factors, such as income, insurance status, access to health care and types of services, and level of caregiver/social support?	4	3
16†	What are the comparative effects of antipsychotics on core disease features in adolescents/young adults with bipolar disorder immediately and in the long term?	4	4
Middle tier			
5	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on health risk behaviors, such as substance use and abuse (including alcohol and tobacco), history of abuse (mental, physical, or sexual), other risk-taking behaviors, diet, and exercise?	4	3
9	What are the comparative safety and effectiveness of using specific antipsychotic classes/agents (e.g., first-generation compared with second-generation antipsychotics) in adolescents/young adults with bipolar disorder?	4	3
17	What are the comparative effects of antipsychotics on commonly associated comorbid conditions and behavioral features (e.g., anxiety disorders, ADHD, substance abuse, sleep disturbance, risk-taking behaviors, or other high-risk behaviors) in adolescents/young adults with bipolar disorder?	4	3
18	What are the comparative effects of antipsychotics on physical, cognitive, and emotional development in adolescents/young adults with bipolar disorder?	4	3
8	How does the likelihood of use of antipsychotic treatment or its comparative safety and effectiveness in adolescents/young adults with bipolar disorder differ depending on the degree of diagnostic certainty for bipolar disorder (e.g., aggressive behavior and disruptive disorders)?	3	3
2	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on psychiatric, medical, and neurodevelopmental comorbid conditions?	2	2
Lower tier			
1	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on illness-specific factors, such as phase, severity, and presence of suicide-related behaviors?	1	1
6	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on medication adherence and factors influencing adherence (e.g., attitudes of caregivers and patients and perceptions of stigma and acceptance)?	1	1
22	What are the comparative effects of antipsychotic classes/agents on adherence to and persistence with drug therapy in adolescents/young adults with bipolar disorder?	1	1
7	How do the comparative safety and effectiveness of antipsychotic treatment in adolescents/young adults with bipolar disorder differ depending on genetic differences?	0	0
10	What are the comparative safety and effectiveness of differences in formulation, dose, and dosing interval of antipsychotic drugs in adolescents/young adults with bipolar disorder?	0	0
20	What are the comparative effects of antipsychotics on suicide-related behavior and nonsuicidal self-injury in adolescents/young adults with bipolar disorder?	0	0
21	What are the comparative effects of antipsychotics on health care utilization and costs in adolescents/young adults with bipolar disorder?	0	0

ADHD = attention-deficit hyperactivity disorder.

* Numbering of questions corresponds to their numbering in the PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) format.

† Questions 3 and 4, which are categorized in the top tier, each received a score of 4, the same as some middle-tier research needs. During the prioritization process, 2 stakeholders suggested that these 2 questions were similar enough to be merged. If these questions had been combined, this broader research need would have received 8 points from 4 stakeholders, so we deemed it appropriate to include questions 3 and 4 in the top tier to ensure full consideration by the Patient-Centered Outcomes Research Institute advisory panel. Question 16 also received a score of 4 but was distinct from the middle-tier questions in that it was selected by 4 stakeholders rather than 3. We therefore included it in the top tier to ensure full consideration.