Bipolar Disorders

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EDITORIAL

Research on Youth With and at Risk for Bipolar Disorder: A 5-Year Update

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1 | Introduction

Bipolar disorder (BD) affects up to 4% of youth and is a leading cause of disability in this age group worldwide [1]. Early-onset BD is associated with a more severe clinical course compared to adult-onset cases, including a higher frequency of mood episodes, longer mood episodes, and greater delay in diagnosis and treatment [2]. These youth are also at an elevated risk for suicide, with studies indicating that as many as one in five youth with BD will attempt suicide [2]. Youth BD is also associated with high rates of psychiatric comorbidities, including anxiety disorders, substance use disorders, and attention-deficit/hyperactivity disorder (ADHD). In addition to the substantial burden of psychiatric symptoms, youth with BD are at an increased risk for early-onset cardiovascular disease, a once-neglected topic that has gained recognition in recent years [2].

Adding insult to injury, youth with BD often face substantial stigma, including-perhaps most concerning-stigma from healthcare providers. This stigma contributes to incorrect and/or delayed diagnosis and treatment avoidance/nonadherence. Reluctance to diagnose and treat BD among youth early in its course exacerbates the impact of BD on the affected youth, leading to more severe long-term outcomes, such as disrupted psychosocial development and impaired academic performance. These long-term consequences underscore the importance of early and accurate diagnosis and intervention. There remains a controversy among researchers around the diagnosis of pediatric BD, leading to polemic perspectives in the literature that further contribute to the stigma that patients and caregivers face [3, 4].

One of the perplexing realities regarding youth BD research is the persistence of controversy despite a substantial accumulation of high-quality research on this topic. While the popularity of this topic within the public domain has waned, and the number of research groups dedicated to progress in this area remains sparse, annual research outputs on youth BD continue to grow. To distill the volume, content, and implications of recent research, we set out to address this gap by conducting a comprehensive review of the literature from the past 5 years. We categorized studies by theme, country of origin, and year of publication to illustrate trends in the field and highlight areas where further research is needed.

2 | Methods

We performed a systematic search of MEDLINE to identify studies published between 2019 and 2023 that included terms related to both bipolar disorder ("BD" OR "bipolar disorder" OR "bipolar" OR "mania" OR "manic" OR "hypomania" OR "hypomanic") and youth ("teen" OR "teenager" OR "teens" OR "youth" OR "children" OR "adolescent" OR "pediatric"). The search was limited to English-language studies involving human participants.

Studies were included if they presented original data and focused specifically on youth with BD or youth at high risk for BD. Studies were excluded if they were reviews, meta-analyses, case reports, editorials, or commentaries, or if the mean age of the study sample was ≥ 22 years without a separate group for youth. Two reviewers independently screened the articles for eligibility.

To provide context for the BD literature, we also undertook a parallel comparison search consisting of: "youth" (as defined above) and "ASD" ("ASD" or "autistic disorder" or "autism spectrum disorder" or "Asperger syndrome" or "autism" or "disorder, autistic" or "Asperger disease" or "Asperger disorder") (limit to English, humans, and 2019–2023).

3 | Results

The initial search yielded 2713 articles. After removing duplicates, 2697 unique citations were screened, and 328 studies met the inclusion criteria. Among these, 207 studies focused on youth with BD as the primary study sample, 106 examined youth at high risk for BD, and 15 studies included both groups. By comparison, there was more than fourfold greater research output for ASD over the same interval, with 11,693 articles. We ran a secondary search using the same terms in PsycInfo and found a similar number of unique citations (N=2027).

The number of publications per year showed a steady increase, with 55 articles in 2019, 60 in 2020, 62 in 2021, 76 in 2022, and 75 in 20. The average number of publications per year was 65.6 ± 9.4 articles, and the increase in annual publications between 2019 and 2023 was 36%.

Geographically (as determined by location of corresponding author), there were 21 countries represented. The majority of studies originated from the United States ($n = 141$, 43%), followed by Canada ($n = 64$, 20%) and China ($n = 30$, 9%). Figure 1 illustrates the distribution of articles by country. The most commonly studied research themes (Figure 2) were neuroimaging and/or neurocognition ($n = 155$, 47%), clinical characterization of youth BD ($n = 125$, 38%), and pharmacological and/or psychosocial treatments ($n = 56$, 17%). Longitudinal studies accounted for 84 articles (26%). Of the treatment studies, 30 examined pharmacotherapy (11 randomized controlled trials [RCTs]), 20 examined psychotherapy (10 RCTs), and 6 examined natural health products (e.g., omega-3 fatty acids, *N*-acetylcysteine; 4 RCTs).

4 | Discussion

Youth BD is among the most complex and challenging medical conditions. Despite currently available pharmacological and psychosocial treatments, youth with BD remain symptomatic over 50% of the time year over year [5]. Progress relies on novel insights regarding the epidemiology, etiopathology, and treatment of youth BD. The current review demonstrates an upward trend of international research outputs on this topic. However, the absolute volume of research is only 207 studies in the past 5 years, less than one quarter of the ASD research literature over the same time interval. Even fewer studies ($n = 106$) address youth at risk for BD, a population for which preventive efforts have arguably the highest potential value. The field of youth BD remains significantly behind other psychiatric disorders, in terms of both volume and scope of research. Although the increase in publications is encouraging, progress is too slow relative to the pressing need for better treatment strategies and interventions. The consequences of untreated or poorly managed BD in youth, including high suicide risk, pronounced functional impairment, and cardiovascular disease risk, demand that research in this area accelerate beyond the current pace.

It is striking that over the past 5 years only 56 studies have been published regarding treatment of youth BD (30 pharmacotherapy, 20 psychotherapy), of which a small minority were RCTs. Although there is a strong evidence base of treatment studies for mania in youth, there are only 10 RCTs published on bipolar

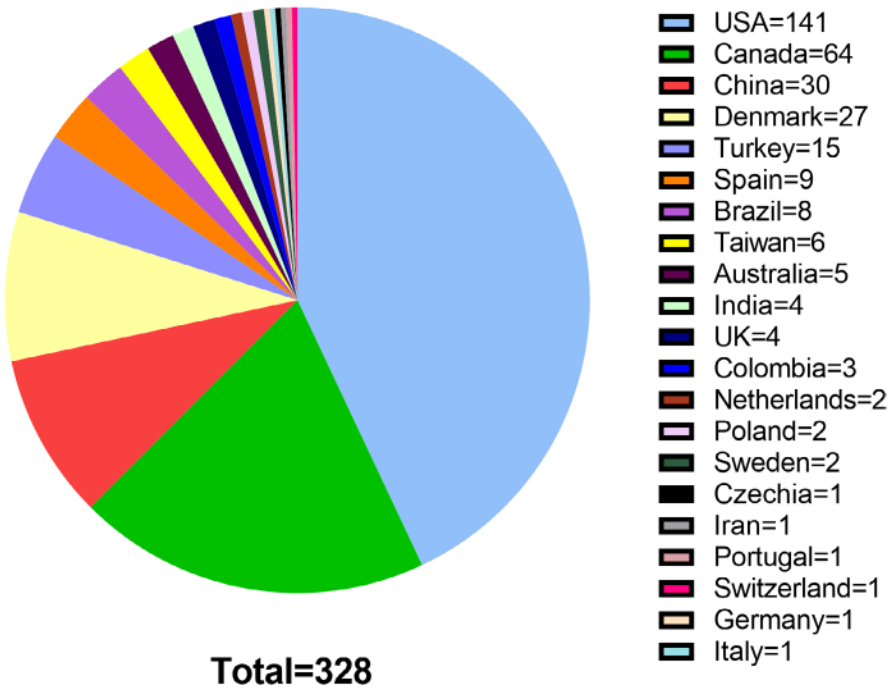

FIGURE 1 | Countries where the included articles were published from.

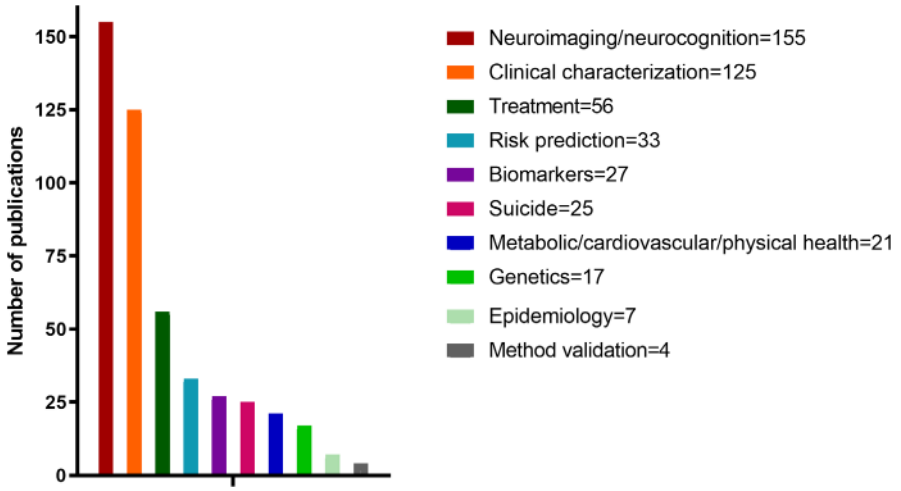

FIGURE 2 | The research topics of included articles.

depression in youth. Moreover, even with multiple RCTs focused on acute manic/mixed episodes, there are not yet RCTs focusing on treatment-refractory mania. Notably, even though comorbid anxiety is prevalent in up to 80% of youth with BD, and despite the fact that anxiety persists even following remission of mood symptoms, there are no RCTs examining treatment of comorbid anxiety among youth BD. While there is a paucity of youth BD clinical trials in general, we wish to highlight three inter-related themes in particular that have been neglected:

4.1 | Maintenance Treatment

A significant gap exists in understanding effective maintenance treatments, which are crucial for preventing relapse and mitigating the chronicity of BD. Current research primarily focuses on acute interventions, while the need for long-term strategies to sustain stability and prevent recurrence of mood episodes is still underexplored.

4.2 | Suicide Prevention

Given the high suicide risk associated with BD and the significant burden of psychiatric comorbidities, it is critical that future research shifts its focus toward developing and validating evidence-based treatments. Preliminary results from psychosocial interventions such as dialectical behavior therapy (DBT) have shown promise for improving emotion dysregulation and decreasing suicide risk among youth with and at risk for BD. However, replication of these findings is warranted and larger trials are needed to assess effectiveness across diverse clinical settings, in different countries, and longitudinally. Suicide prevention strategies must be a focus of future studies, as youth with BD remain at high risk for suicide.

4.3 | Vascular Interventions

Finally, despite the growing number of studies demonstrating adverse vascular health indices among youth with BD, there are still no *vascular intervention trials* aside from one exercise study. Treatments targeting cardiovascular risk factors (e.g., obesity, hypertension) and vascular health remain understudied despite their potential to improve both physical and psychiatric outcomes in youth with BD. Indeed, preliminary literature among adults highlights the potential value of several cardiovascular drugs on both brain and mental health, and we hope to see more studies of these interventions among youth with BD.

To improve outcomes for youth BD, there must be a concerted effort to attract more researchers to the field, including established researchers and new researchers. Cultivating a new generation of researchers with a focus on youth BD will be especially critical for ensuring sustainable research efforts. Although there were 21 countries represented, the United States and Canada accounted for over 60% of the published studies. In contrast, research from low- and middle-income countries is sparse. This lack of international representation limits the generalizability of the findings and poses significant challenges in understanding the broader implications of BD in diverse populations. Youth in low- and middle-income countries may face unique stressors, such as limited access to mental health services, and higher rates of undiagnosed or untreated BD, resulting in even poorer long-term outcomes. It is essential for future research to explore how socioeconomic and cultural differences impact the clinical presentation, treatment, and course of BD among youth. Here, we have highlighted three core treatment themes. However, there are many other themes that are both under-studied and crucial for progress, including neuromodulation, personalized treatment approaches, and exercise interventions just to name a few.

To move toward a future where there are more youth BD researchers, conducting an increasing amount of studies, representing a diversity of countries and regions, there is a need for a substantial increase in research funding and infrastructure. The establishment of dedicated funding streams for youth BD research is essential to drive innovation and retain a specific focus on this understudied population that has multiple sources of risk for suboptimal mental health and physical health outcomes. By fostering collaborations across disciplines and countries, and by providing sufficient resources, we can accelerate the pace of discovery and, ultimately, improve outcomes for youth with BD.

Despite advancements in understanding youth BD, a critical gap persists between research findings and clinical practice. This disconnect is especially problematic given that multiple clinical scenarios have yet to be studied in youth BD clinical trials, and for which treatment therefore proceeds with limited empirical evidence. Translating research findings into practice involves several obstacles, including limited implementation of findings from clinical trials, underutilization of preventative interventions, and a paucity of standardized care guidelines tailored for this youth population. Even as research on BD expands, clinical settings often lack the resources or infrastructure necessary to integrate research findings effectively. This issue perpetuates a delay in adopting best practices and limits access to innovative treatments that could reduce suicide risk and cardiovascular risk.

A core strategy crucial for advancing all the aforementioned themes is collaboration and partnership with consumer advocates. There are local, national, and international consumer advocacy groups that provide hope, support, and reliable information for youth with BD and their families. Nonetheless, thus far collaboration and partnerships between patients, families, treatment providers, researchers, policymakers, and funders focused on youth BD has yet to realize its potential. As previously mentioned, the amount of autism research is vastly greater than youth BD research. We note that *Autism Speaks*, the autism consumer advocate community, has been successful in establishing meaningful partnerships with researchers and funding streams that support collaborative projects. With annual research funding of over $20 million USD, this organization has clearly changed the landscape of autism research for the better, yielding significant progress. Relatedly, this community has also been successful in establishing the Autism Cares Act. While no approach is perfect, and there are differences between autism and BD, we believe that there have been meaningful successes in the field of autism owing to this organization's efforts, and that similar successes in the field of youth BD are urgently needed.

In conclusion, addressing the pressing challenges in youth BD research is critical for advancing both clinical care and public health outcomes. Despite encouraging growth trajectory in research outputs, youth BD research lags behind other major psychiatric disorders, such as autism. This gap in research, particularly in the areas of maintenance and comorbidity treatment, suicide prevention, and vascular interventions, underscores the urgent need for more targeted studies that can improve long-term outcomes for youth with BD. Additionally, gaps in international representation in research limits our understanding of BD in diverse populations. Collaborative efforts across countries and disciplines, as well as partnerships with consumer advocates, are essential to drive progress in the field. It is imperative to expand the community of researchers dedicated to this topic. Such an expansion will require substantial investment from federal, foundation, and philanthropic sources to expedite the recruitment and retention of the next generation of youth BD researchers. By increasing funding, fostering global collaborations, and integrating insights from the autism research community, we can ensure that research focused on youth BD accelerates and leads to tangible improvements in the lives of those affected.

Conflicts of Interest

Dr. Benjamin I. Goldstein acknowledges his position as RBC Investments Chair in Children's Mental Health and Developmental Psychopathology at CAMH, a joint Hospital-University Chair between the University of Toronto, CAMH, and the CAMH Foundation. Dr. Mikaela K. Dimick is the recipient of a Postdoctoral Award from the Canadian Institutes of Health Research. All other authors report no actual or potential conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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