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Invited Review

Evidence-based Psychopharmacological Treatments for Pediatric Bipolar Disorder

Pediatrik Bipolar Bozukluk için Kanıta Dayalı Psikofarmakolojik Tedaviler

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ABSTRACT

Bipolar disorder is a chronic illness that often onsets in early stages of life, and the first episode of bipolar disorder frequently occurs in adolescence. Pediatric bipolar disorder (PBD) has more severe symptoms and a poorer prognosis compared to bipolar disorder in adults. Due to limited data on the psychopharmacological treatment of PBD, children and adolescents have been treated primarily in consideration of the findings obtained from clinical studies performed in adults. The efficacy of the psychotropic agents seems to differ in children and adolescents compared to adults. The evidence-based psychopharmacological treatment modalities of PBD are of growing interest in children and adolescents. This review discusses current Food and Drug Administration approved medications for PBD and guidelines for PBD. The psychopharmacologic evidence and algorithms of PBD treatment relevant to different stages of bipolar disorder, including acute manic/mixed episodes, bipolar depression, and maintenance treatment are examined in this review article.

Keywords: Bipolar disorder, mania, psychopharmacology, mood disorders, child and adolescent, bipolar depression

ÖZ

Bipolar bozukluk sıklıkla yaşamın erken dönemlerinde başlayan kronik bir hastalıktır ve bipolar bozukluğun ilk atağı sıklıkla ergenlik döneminde ortaya çıkar. Pediatrik bipolar bozukluk (PBB), yetişkinlerdeki bipolar bozukluğa göre daha şiddetli semptomlara ve daha kötü prognoza sahiptir. Çocuklar ve ergenler, PBB'nin psikofarmakolojik tedavisine ilişkin verilerin sınırlı olması nedeniyle, öncelikle yetişkinlerde yapılan klinik çalışmalardan elde edilen bulgulara göre tedavi edilmektedir. Psikotrop ajanların etkinliği çocuklarda ve ergenlerde yetişkinlere göre farklılık gösteriyor gibi görünmektedir. PBD'nin kanıta dayalı psikofarmakolojik tedavileri çocuklarda ve ergenlerde giderek artan bir ilgi görmektedir. Bu derlemede PBB için mevcut Amerikan Gıda ve İlaç İdaresi onaylı ilaçlar ve PBB ile ilgili kılavuzlar tartışılmaktadır. Ayrıca, akut manik/karma dönemler, bipolar depresyon ve idame tedavisi dahil olmak üzere bipolar bozukluğun farklı evrelerine bağlı olarak PBB tedavisine ait psikofarmakolojik kanıtlar ve algoritmalar incelenmektedir.

Anahtar kelimeler: Bipolar bozukluk, mani, psikofarmakoloji, duygudurum bozuklukları, çocuk ve ergen, bipolar depresyon

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INTRODUCTION

Bipolar disorder is a chronic, severe psychiatric condition associated with poor outcomes and it frequently requires lifelong treatment consisting of pharmacotherapy and psychosocial interventions[1]. Bipolar disorder affects over 1% of the global population, regardless of nationality, ethnicity, or socioeconomic status, and stands as one of the primary contributors to disability among the youth population[2]. Early diagnosis of pediatric bipolar disorder (PBD) in youth is crucial because nearly 60% of individuals with PBD are affected before the age of 21 years[3].

Diagnostic criteria for PBD in children and adolescents are the same as for adults, but diagnosis of early-onset PBD is more challenging than late-onset PBD. Temper outbursts and irritability commonly develop in youth and more frequently cause mixed or rapid-cycling presentations compared to adults[4]. Moreover, symptoms of mania and hypomania that overlap with symptoms of other psychiatric disorders such as attention deficit and hyperactivity disorder (ADHD), personality disorders, and behavioral problems in young people complicate the diagnosis of PBD[5]. Disruptive mood dysregulation disorder (DMDD) was included in the Diagnostic and Statistical Manual of Mental Disorders-The Fifth Edition

(DSM-5) to address concerns "about the appropriate diagnosis and treatment of children and adolescents who present with chronic, persistent non-episodic irritability relative to children and adolescents who present with classical bipolar disorder" and to put right what was evaluated as an inappropriate overdiagnosis of BPD in some children[6,7]. Youngsters with DMDD who have higher psychiatric comorbidity rates are also debilitated and have functional impairments in different areas[8]. Although the inclusion of the diagnostic criteria of DMDD in DSM-5 has reduced the incidence of overdiagnosis in youth with BPD, antipsychotics and polypharmacy have been started to be used more frequently in these children and adolescents[6]. It is important to emphasize that while there are no treatment guidelines for DMDD, children and adolescents with persistent aggression and non-episodic irritability remain a challenging group[9]. Episodes of acute mania correlate with engaging in high-risk activities, including gambling, substance abuse, accidents, and hazardous behaviors. Episodes of depression are linked to a heightened risk of suicide[4]. PBD is associated with more severe symptoms, suicide risk, and poorer prognosis compared with the late- onset PBD. The efficacy of psychopharmacological treatments seems to differ in children and adults. Therefore, there is a growing interest in identifying effective and safe psychopharmacological treatments for PBD in children and adolescents[10].

Pharmacotherapy of bipolar disorder in children can be challenging. The crucial step in the pharmacotherapy of PBD is to confirm the PBD episodes and define the patient's mood status because medical approach to mania, hypomania, and depression changes considerably[11]. Thus, the choice of pharmacotherapy is generally based on the presentations of PBD (manic/mixed, depressive, or maintenance). Children and adolescents have been treated primarily by adjusting findings from clinical studies in adults due to limited data on the psychopharmacological treatment of PBD in children. The National Institute for Health and Care Excellence (NICE) proposes recommendations on treating specific conditions covered by The National Health Service in the United Kingdom. Relevant NICE guidelines published in 2014 cover management strategies for patients with bipolar disorders in adults, children, and adolescents in primary and secondary care[12]. In 2018, the last updates of The Canadian Network for Mood and Anxiety Treatments (CANMAT) were published in collaboration with the International Society for Bipolar Disorders (ISBD). CANMAT 2018 guidelines have used recommendations for the first, second, and third-line treatments, considering levels of evidence for efficacy and clinical support based on experience[13]. The latest American Academy of Child and Adolescent Psychiatry (AACAP) algorithm for the psychopharmacological treatment of PBD was still based on the results of randomized controlled trials (RCTs) performed in adult patients, data from open-label trials and retrospective studies conducted in children and adolescents[14]. Since 2005, an increasing number of RCTs have been performed to investigate the efficacy of psychotropic drugs in the treatment of PBD. Recently, Hobbs et al.[15] have proposed a comprehensive update to the AACAP's 2005 algorithm for PBD treatment.

This review discusses FDA approved medications for PBD and current guidelines related to PBD. Moreover, we have examined the psychopharmacologic evidence and algorithms of PBD treatment depending on the manifestations of illness.

FDA-approved Psychotropic Drugs for The Treatment of Pediatric Bipolar Disorder

Most of the RCTs of psychotropic agents used in the treatment of PBD have been reported, especially in the last two decades. Medications superior to placebo in the treatment of BPD patients presenting with acute manic or mixed episodes include aripiprazole[16], asenapine[17], risperidone[18], quetiapine[19], and olanzapine[20]. FDA has approved aripiprazole, asenapine, risperidone, or quetiapine for their use in the management of acute mania or mixed episodes in PBD for patients aged ≥10 years and olanzapine for adolescents aged 13-18 years. The FDA has approved lithium for the treatment of manic or mixed episodes of PBD in individuals aged 7-17 years, supported by favorable outcomes observed in RCTs performed in children and adolescents[21]. None of the anticonvulsant medications (valproate, carbamazepine, lamotrigine) are currently approved by the FDA for the treatment of PBD[22,23]. Lurasidone and olanzapine/fluoxetine combination have been approved for the treatment of depressive episodes of PBD in children aged 10-17 years[24,25]. Lithium and aripiprazole are the only two medications to be used with an FDA indication for the maintenance treatment of PBD.

Treatment of Acute Manic or Mixed Episodes

Acute episodes have a significant risk of suicide, disinhibition, recklessness, irritability, and threat to family or others. Accordingly, the primary objectives involve ensuring the safety of the patient and those in the community while striving for clinical stability with

minimal adverse effects in the acute management of PBD. Additionally, fostering engagement and establishing a therapeutic agreement are crucial aspects of managing this lifelong condition. Collaborative efforts are vital for long-term adherence to PBD treatment, especially during the initial episode[26].

There are several published guidelines for the treatment of acute PBD episode[12-14]. NICE 2014 guidelines indicate that differences in dosage and side effects of the medications in younger patients compared to the adult population should be taken into account[12]. Mechanisms of action of second-generation antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) and mood stabilizers (lithium, sodium valproate, lamotrigine, carbamazepine) are thought to be similar in youths and adults[12]. At the time of the publication of NICE 2014 guidelines, only one drug (aripiprazole) was licensed for the treatment of moderate to severe manic episodes in bipolar disorder in children aged 13 years and older for the duration of 12 weeks, and some preparations of lithium were also licensed for use in children aged over 12 years in the UK[27]. At the time of release of NICE guidelines in September 2014, olanzapine, risperidone, haloperidol, quetiapine, lamotrigine, lithium, and valproate lacked UK marketing authorization for use in children and young people for treating mania or hypomania. However, the NICE 2014 guidelines suggested consideration of the recommendations intended for adults in such cases[12]. In accordance with recommendations for adult patients, if a patient experiences mania or hypomania while on antidepressant monotherapy, it is advised to discontinue the antidepressant and consider initiating treatment with an antipsychotic drug such as haloperidol, olanzapine, quetiapine, or risperidone[12]. If the initial antipsychotic drug is poorly tolerated or ineffective at maximum dosage, an alternative antipsychotic drug from the recommended list should be offered[12]. While off-label use of lithium was acknowledged in September 2014, NICE suggested that if a second antipsychotic drug fails to provide sufficient relief at maximum dosage, the addition of lithium may be considered[12]. If the addition of lithium proves ineffective or if lithium is unsuitable due its adverse effects on biochemical parameters detected during routine blood tests, valproate may be considered as an alternative[12]. Furthermore, the updated NICE 2023 guidelines advise against initiating valproate treatment for the first time in patients, regardless of gender, who are younger than 55 years old[28].

The CANMAT and the ISBD 2018 guidelines emphasize the significance of evidence levels with clinical support for efficacy in formulating the final treatment recommendations, as outlined in Table 1[13]. These guidelines recommend lithium, risperidone (level 1 evidence), aripiprazole, asenapine, and quetiapine (level 2 evidence) as the first-line options for acute treatment of PBD[13]. Risperidone is recommended for the treatment of non-obese youth and children with ADHD as a preferred alternative to lithium. Olanzapine (level 2 evidence) and ziprasidone (level 2 evidence) are offered as second-line options in consideration of safety and tolerability concerns. Adjunctive therapy with quetiapine is also recommended as a second-line treatment (level 3 evidence)[13]. Despite insufficient response rates observed with divalproex, positive treatment outcomes documented with this drug in open-label studies involving children, and adolescents together with its extensive history of use among adults with bipolar disorders, position it as a third-line treatment alternative for youths who do not respond to or could not tolerate first or second-line treatment options (level 4 evidence)[29]. Oxcarbazepine has failed to demonstrate superiority over a placebo in a significant RCT (level 2 negative evidence) and has not been endorsed in the CANMAT and ISBD 2018 guidelines[13,30].

The most recent update in psychopharmacological treatments for PBD highlighted the evidence that

Table 1. Definitions for line of treatment ratings in guidelines

Treatment	Evidence levels
First-line	Level 1 or level 2 evidence for efficacy plus clinical support for safety/ tolerability and no risk of treatment-emergent switch
Second-line	Level 3 or higher evidence for efficacy plus clinical support for safety/ tolerability and low risk of treatment-emergent switch
Third-line	Level 4 evidence or higher for efficacy plus clinical support for safety/ tolerability
Not recommended	Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018 guidelines[13]

has emerged since the AACAP 2005 algorithm was published for managing manic or mixed episodes in children and adolescents[15]. Hobbs et al.[15] suggested use of second-generation antipsychotic agents (SGAs) as the first-line treatment of acute manic or mixed episodes, with the specific choice of antipsychotic agent left to the discretion of the clinician. The latest update has emphasized better efficiency of SGAs compared to other agents used in RCTs for the treatment of mixed or manic episodes of PBD[15]. For the treatment of manic or mixed episodes of PBD associated with psychosis, the initial approach involves using one of the FDA-approved SGAs such as aripiprazole, asenapine, olanzapine, quetiapine, or risperidone[15]. If there is no response to the priorly preferred SGA, another FDA-approved SGA can be used as monotherapy[15]. Lithium augmentation may be considered in case of partial response to two SGAs. In cases of acute manic or mixed episodes without psychosis, lithium may be considered as an augmentation therapy to an SGA or as monotherapy if two different SGAs[15] fail to provide an adequate response[15]. During acute manic or mixed episodes with psychotic or non-psychotic manifestations it is advisable to contemplate incorporating lamotrigine as an adjunctive therapy alongside an SGA and/or lithium[15]. If tolerance to lithium and lamotrigine is not encountered, it is advisable to consider enhancing the treatment regimen by combining an SGA with second-line agents such as divalproex, carbamazepine, or oxcarbazepine[15]. If patients do not respond to these agents, electroconvulsive therapy (ECT) or clozapine can be considered for both psychotic and nonpsychotic groups of acute manic or mixed episodes[15]. Even though lithium has showed a smaller effect size compared to SGAs in RCTs performed for the treatment of manic or mixed episodes of PBD[15], it remains as an important treatment option due to its unique features which include reducing suicidality in adults and children and providing neuroprotective advantages both *in vivo* and *in vitro*[31].

Treatment of Depressive Episodes

Children with PBD usually exhibit depression as the initial mood episode; however, a diagnosis of PBD requires a history or presence of mania/hypomania associated with an elevated risk of self-harm and suicide[32]. The Course and Outcome of Bipolar Youth study has revealed that, during follow-up, the majority of recurrences after an initial episode of BPD were major depressive episodes (60%), followed by hypomanic (21%), manic (15%), and mixed (5%) episodes[4]. Patients with depressive episodes of PBD are more frequently inclined to exhibit more severe psychiatric comorbidity, atypical features, psychotic features, a heightened risk of suicide, subsyndromal manic symptoms, and a higher prevalence of positive family history compared to those with unipolar depression[33]. While selective serotonin reuptake inhibitors (SSRIs) can enhance depressive symptoms in bipolar disorder, they also elevate the risk of triggering a manic episode[34]. In addition, some reports indicate a higher occurrence of antidepressant-induced switching to mania in children and adolescents compared to adults[35]. Healthcare providers should approach the use of antidepressants in depressive episodes of PBD with caution[14,34].

The 2014 NICE guidelines indicate lack of empirical data on the treatment of depressive episodes in PBD among children and adolescents[12]. When the NICE 2014 guidelines were released, there were no trials of SSRIs in bipolar depression. However, it was noted that open-label treatment trials of lithium[36] and lamotrigine[37] might be effective in addressing depressive episodes in PBD. The NICE 2014 guidelines propose referring to the recommendations for adults when addressing depressive episodes in PBD[12]. According to the adult recommendations, in cases of moderate or severe bipolar depression and the absence of bipolar disorder treatment, fluoxetine combined with olanzapine or quetiapine alone can be offered based on the individual's preference and prior treatment response[12]. If there is no response to fluoxetine-olanzapine or quetiapine combination, the consideration of lamotrigine monotherapy is advised[12].

Data on pediatric populations are limited, and their interpretation is complicated by the presence of elevated placebo-response rates obtained in RCTs. In other words, the observed improvements in symptoms might be influenced by the placebo effect rather than the actual effectiveness of the tested treatment. As a result, the CANMAT and ISBD 2018 recommendations primarily rely on the clinical experience and results obtained from adult studies[13]. In an RCT study, DelBello et al. found that lurasidone induced a higher response rate than placebo (level 2 evidence) in alleviating depressive symptoms in the pediatric population with acute bipolar depression[25]; but still we have insufficient clinical data regarding its use in the pediatric population. Due to clinical experience and its effectiveness in adult patients, lurasidone is suggested as a first-line treatment for depressive episodes in PBD[13]. Meanwhile, lithium

and lamotrigine are proposed as first-line treatment options for bipolar depression in adults[13]. Despite the limited RCT data, there is extensive clinical experience with these medications. Results of open-label studies with lithium (level 4 evidence)[36] and lamotrigine (level 4 evidence)[37] in children and adolescents are available. Based on the robust evidence in adults, lithium and lamotrigine are advised as second-line treatment options for PBD depression. Additionally, there is RCT level 1 evidence supporting the theraupetic effectiveness of the olanzapine-fluoxetine combination for PBD depression[24]. However, concerns about the metabolic effects of olanzapine and insufficient clinical experience with this combination treatment in pediatric patients have led to the classification of this option as a third-line treatment alternative[13]. Considering the negative results in children and adolescents (level 2 negative evidence)[38,39], quetiapine is recommended as the third-line treatment for the pediatric population due to evidence supported by significant clinical experience from studies performed in adults. Observational studies advocate for the cautious use of antidepressants in PBD and suggest their combination with mood stabilizers (level 4 evidence)[40,41]. Oxcarbazepine is not approved for the management of depressive episodes of PBD and has not been found to have a higher response rate than placebo (level 2 negative)[13]. However, a large-scale RCT has showed its effectiveness in younger children rather than older individuals[30].

The most recent update of AACAP 2005 proposes lurasidone as a first-line treatment for depressive episodes of PBD[15]. Lurasidone (effect size, 0.45) and olanzapine-fluoxetine (effect size, 0.46) combination are both FDA-approved drugs. However, lurasidone has a lower metabolic side effect burden than olanzapine-fluoxetine combination[24,25]. This updated review suggests that lurasidone, if partially effective, can be combined with lamotrigine[15]. If depressive symptoms persist during adjunctive therapy with lamotrigine, adding an FDA approved SSRI such as escitalopram or fluoxetine may be considered; however, caution is warranted due to the risk of a manic switch[15]. If lurasidone fails to elicit a response, cross-tapering to the olanzapine-fluoxetine combination should be considered[15]. Despite evidence of efficacy and FDA approval, the underuse of olanzapine-fluoxetine persists in clinical practice. For partial responders to olanzapine-fluoxetine combination, augmentation with lamotrigine is recommended[15]. If FDA-approved agents have failed, non-FDA-approved treatments like quetiapine, risperidone, asenapine, aripiprazole, bupropion, other SSRIs, and lithium should be considered [15]. SSRIs should be used along with mood stabilizers to mitigate the risks of manic switch. Clinicians should note that quetiapine is FDA-approved only for adults; in children and adolescents with bipolar depression, it showed similar efficacy to placebo in two RCTs[38,39]. While not recommended as a first-line medication for youths, quetiapine remains an acceptable choice for older adolescents suffering from bipolar depression[15]. In cases where other treatments prove ineffective, ECT may be considered as an alternative option[15].

Maintenance Treatment

PBD presents a chronic illness trajectory with a high susceptibility to relapse and permanent disability. A 5-year prospective follow-up study on adolescents with bipolar disorder reported relapse rates of 44%[42]. Effective long-term treatments of bipolar disorder are essential, particularly in youths. Despite the severity and chronicity of PBD, research in the psychopharmacology of maintenance treatment of PBD has provided insufficient evidence than in adult bipolar disorder[43].

In clinical practice, long-term treatment of PBD often includes the off-label use of antipsychotics and anticonvulsants since there is a paucity of randomized data available on maintenance treatment in youths with PBD[44]. There are several published guidelines for the maintenance treatment of PBD. For long-term pharmacological treatment, the 2014 NICE guidelines advise considering medications that have demonstrated efficacy during episodes of PBD[12]. The NICE guidelines advise engaging in a discussion with the individual about their preference to either continue with this treatment or switch to lithium therapy[12]. NICE guidelines recommend the use of lithium as a first-line maintenance treatment of PBD[12]. If lithium is ineffective, poorly tolerated, or not suitable, an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine, or risperidone) may be considered[12]. If the initial antipsychotic is not well tolerated at any dosage or proves ineffective at the highest dosage, it is advisable to contemplate using a second antipsychotic from the list of recommended medications[12]. According to the NICE guidelines, if the second antipsychotic is ineffective, a combination of valproate with either an antipsychotic or lithium should be considered[12]. It is recommended that when long-term pharmacological treatment is terminated, the patient should be educated on how to recognize early signs of relapse and what to do at the time of recurrence [12]. Additionally, the NICE guidelines suggest continuing

to monitor symptoms, mood, and mental status for two years after the medication is completely discontinued[12].

CANMAT and ISBD 2018 guidelines recommend aripiprazole (level 2 evidence)[45,46], lithium (level 2 evidence)[47], and divalproex (level 2 evidence)[48] as first-line maintenance treatment alternatives of PBD. The CANMAT guidelines indicate that a minority of patients continue to do well after switching to either lithium or divalproex monotherapy, and the majority respond positively when the combination therapy is reintroduced [13]. Additionally, studies have suggested the effectiveness of combination therapy, such as risperidone plus lithium or divalproex[49], and lithium plus divalproex or carbamazepine[50], in achieving and sustaining remission. Use of lamotrigine may also be considered as an adjunctive therapy for those aged ≥13 years (level 2 evidence)[51]. However, there is no recommendation with level ≥3 evidence for second-line maintenance therapy. As for asenapine, there is limited data for its use as long-term PBD treatment alternative. Nonetheless, an open-label study suggests gradual tapering of its dose during treatment of manic symptoms over 50 weeks in the pediatric patients (level 4 evidence). Additionally, a RCT conducted in adult patients has validated the effectiveness of asenapine in preventing the recurrence of mood episodes. Clinical observations and open-label studies suggest that quetiapine, risperidone, or ziprasidone may serve as alternative third-line alternatives for maintenance treatment, especially for patients who has shown positive responses during acute episodes of PBD (level 4 evidence)[52-54].

The AACAP 2005 guidelines suggest that mood stabilizers (carbamazepine, lamotrigine, lithium, and valproate) along with SGAs can be used as first-line and combinations of these medications as second-line treatment alternatives[14,22]. The AACAP 2005 guidelines suggest use of SGAs as adjunctive agents or alternatives to lithium and valproate[1]. According to AACAP practice parameters, maintenance treatment for at least 12-24 months following the initial episode is recommended [14]. For patients with severe symptoms and a history of recurrent episodes, lifelong treatment with psychotropic medications should be considered[14]. Monotherapy with either lithium or divalproex in pediatric patients is associated with a comparatively shorter median time to relapse[55]. Furthermore, discontinuation of lithium has been demonstrated to elevate relapse rates in adolescents diagnosed with bipolar disorder[56]. Hence, gradual tapering, and finally discontinuation of maintenance therapy is recommended over a period of time devoid of significant anticipated stressors[14]. The American Psychiatric Association's Practice Guideline for the Treatment of Patients with Bipolar Disorder in adults advises that maintenance therapy with an agent should persist for at least 18 months following the stabilization of a manic episode[57]. Since definitive answers are not available on the exact duration of maintenance treatment, clinicians must navigate the balance between the potential harm of symptom recurrence and the side effects of mood stabilizers and antipsychotics. This uncertainty persists due to the lack of conclusive information regarding the long-term effects of these medications[1].

Only lithium[47] and aripiprazole[45,46] have been approved by FDA for the maintenance treatment of PBD. Numerous international treatment guidelines advocate initiating treatment for PBD with monotherapy and suggest that the drug combinations are considered only after multiple conservative treatment approaches have proven ineffective[1,13]. A recent meta-analysis examining long-term treatment trials for PBD has revealed that combination treatments, which typically involve use of lamotrigine, lithium, or valproate combined with a SGA, yield superior outcomes compared to monotherapy trials[44]. This meta-analysis has formulated the apparent order of efficacy as follows: combined agents > anticonvulsants ≥ lithium ≥ antipsychotics[44]. Nevertheless, conduction of further RCTs is necessary to evaluate long-term safety and effectiveness of these psychopharmacologic agents used for the treatment of PBD. In the context of maintenance treatment for bipolar disorder, the polarity index (PI) serves as a metric indicating the relative preventive efficacy of drugs against manic versus depressive episodes[58]. The PI is derived by calculating the ratio of the Number Needed to Treat (NNT) for the prevention of depression to the NNT for the prevention of mania, as evidenced by results from RCTs performed in adult populations. A PI value exceeding 1.0 signifies relatively greater prophylactic efficacy against manic episodes, while a value below 1.0 suggests relatively greater efficacy in preventing depressive episodes. In the context of maintenance therapy for bipolar disorder, the PI values are as follows: 12.09 for risperidone, 4.38 for aripiprazole, 3.91 for ziprasidone, 2.98 for olanzapine, 1.39 for lithium, 1.14 for quetiapine, and 0.40 for lamotrigine. The reliability of the PI values for valproate and oxcarbazepine may be compromised due to their ineffectiveness in trials of maintenance therapy. Notably, quetiapine and lithium exhibit a PI close to 1, indicating their nearly equal efficacy in preventing both manic and depressive episodes[58]. Indeed, although PI values are derived from adult RCTs, they may still be

clinically beneficial in providing information for the selection of an appropriate maintenance treatment for bipolar disorders in adolescents.

CONCLUSION

This article reviews evidence from different guidelines and algorithms formulated for the psychopharmacological treatment of PBD, acute manic or mixed, depressive episodes, and maintenance therapy. At present, there is still a lack of sufficient double-blind, RCTs involving pediatric and adolescent patients with bipolar disorders. The existing guidelines have predominantly relied on studies conducted on adult patients with bipolar disorders. However, the clinical characteristics and presentation of bipolar disorder in children and adolescents differ significantly from those in adults. This fact highlights the necessity for the conduction of further psychopharmacological trials specifically tailored to this younger age group. As ongoing RCTs are carried out, the body of evidence regarding psychopharmacological treatment in children and adolescents will accumulate. Consequently, there is an ongoing need for updated and evidence-based guidelines that specifically address the treatment of PBD.

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Ethics

Authorship Contributions

Concept: P.U., E.A., Design: P.U., E.A., Data Collection or Processing: P.U., E.A., Literature Search: P.U., E.A., Writing: P.U., E.A.

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