Expert Opinion

Pharmacotherapeutic strategies for pediatric bipolar disorder

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There has been a recent increase in recognition and diagnosis of pediatric bipolar disorder (PBD), along with an increase in prescriptions for psychotropic medications for treating children suffering from this chronic, potentially disabling disorder. Lithium remains the only FDA-approved mood stabilizer for use in children > 12 years of age and along with valproic acid and carbamazepine, forms the triad of traditional mood stabilizers used for initiation of treatment for PBD. There has been a recent surge in the use of atypical antipsychotics in PBD, which may be due to their relative ease of administration and lack of requirement for serum level monitoring. A combination of traditional mood stabilizers along with atypical antipsychotics is commonly used in clinical practice, despite a lack of compelling empirical data. Although there is an urgent need for controlled studies on the available treatment options and strategies in PBD, recent expert consensus guidelines and emerging controlled pharmacotherapy data on PBD will lay the platform for future scientific research in the area.

Keywords: atypical antipsychotic, mood stabilizer, pediatric bipolar disorder

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1. Introduction

Pediatric bipolar disorder (PBD) is a serious psychiatric illness that disrupts the normal development and lives of numerous children and adolescents across the world [1,2]. PBD has a significant impact on the psychosocial functioning of the child. It is not only responsible for significant morbidity and mortality in this age group, but also for impaired relations with family and peers and increased dropouts from school [3,4]. PBD is also associated with significant substance abuse, suicide and legal problems [5,6].

PBD has been estimated to affect ~ 1% of children and adolescents [7]. The use of different diagnostic criteria, the type of clinical setting, the diagnostic instrument used and the presentation of symptoms all have a significant impact on making an early and accurate diagnosis of PBD. A recent study by Youngstrom and Daux, 2005, reported that although PBD was found in ≤ 0.6% of epidemiologic samples, it accounted for 17 – 30% of children in clinical samples [8]. A fair estimate from child psychiatry in-patient units indicates that 30 – 40% of the children hospitalized for psychiatric reasons may suffer from PBD [9].

Although recent years have shown an increase in frequency of diagnosis of PBD, there is still limited understanding of this mood disorder in the pediatric age group. There is evidence to suggest that the diagnosis of bipolar disorder is often delayed or even missed. In a retrospective chart review of youths suffering from bipolar disorder in a community mental health out-patient setting, the mean number of years from the onset of mood symptoms until a diagnosis of bipolar disorder was made was 5 years, with the maximum being 12 years [10]. The reasons for delay in diagnosis included a different presentation from the usual adult presentation, milder cases being considered as a phase of growing up, initial episodes showing more depressive

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than manic symptoms and under-reporting of symptoms by the youths. Furthermore, in patients with early onset bipolar disorder, the rates of remission over 1 year are only 35 – 40% whereas relapse rates remain high at 40 – 50% [11]. In this manner, PBD may have a worse outcome than adult-onset bipolar disorder [12].

2. Diagnosis

The diagnosis of PBD requires a characterization of the type of episode using the Diagnostic and Statistical Manual 4th edition text revision (DSM-IV-TR) criteria [13]. Bipolar I disorder requires the presence of at least one manic episode. A manic episode involves a distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week (or < 1 week if hospitalization is required) and is associated with marked impairment in social/occupational functioning. Mixed episodes are characterized by both manic and depressive symptoms and last for at least 1 week. Bipolar II disorder involves a history of having both depressive and hypomanic episodes in the absence of a clear manic episode. Cyclothymia involves the presence of hypomanic episodes with minor depressive episodes, never meeting the criteria for major depressive episodes. It should also be remembered that depressive symptoms can present as irritability and anger in younger children.

Before treating children with bipolar disorder, it is of course necessary to make an accurate diagnosis of bipolar disorder. PBD may differ in both the presentation and prognosis as compared with bipolar disorder in adults, and thus it can be challenging when applying the DSM-IV-TR diagnostic criteria for bipolar disorder to youth, especially prepubertal children. Prepubertal manic children commonly present with irritability and anger rather than euphoria [14]. Mixed episodes are common in childhood bipolar disorder, which is also associated with increased suicidality and a chronic course that may be more resistant to treatment than the adult form [15].

Bipolar disorder not otherwise specified (BD-NOS) probably represents the largest group of bipolar disorder in the pediatric age group. The difficulty with this diagnosis is that there are no agreed diagnostic criteria, although researchers have made suggestions [16,17]. Usually, this diagnosis is meant to capture children who have rapid mood swings, irritability and fluctuating depressive and euphoric moods, with often poorly defined durations or with too few other manic symptoms to meet DSM-IV criteria for a hypomanic or manic episodes. Although the course of BD-NOS in children is not yet fully understood, early reports indicate that ≤ 30% of these children may progress to bipolar I or II disorder within 3 years [16]. Children who have chronic irritability without other significant manic symptoms should be considered at this time to have severe mood dysregulation and not yet a bipolar spectrum disorder [18,19].

The semistructured and structured instruments available and widely used for diagnosing PBD in research settings include the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS), the Washington University Kiddie and Young Adult SADS and Schizophrenia, the Diagnostic Interview Schedule for Children and the Children's Interview for Psychiatric Syndromes [20-23]. As these research tools may require ≤ 3 h for administration, instruments such as the self-reporting Mood Disorder Questionnaire (validated in adults) [24] and the Young Mania Rating Scale (YMRS) [25] have been frequently used to screen for mania in clinical and research settings. The Child Bipolar Questionnaire, a parent-rated screen with an internal subscale of symptom dimensions, was recently preliminarily found internally reliable and valid against the K-SADS present and lifetime version [26]. The Clinical Global Impressions scale has also been modified for use in bipolar disorder, especially to monitor treatment response (CGI-BD) [27]. Furthermore, there are also parent-rated scales such as the YMRS-parent version, the Parent – General Behavior Inventory (GBI), and the Child Mania Rating Scale [28-30]. There are also self-report measures that are available, including the Adolescent Self Report GBI [29].

The symptoms and course of bipolar disorder in childhood are often complicated by co-morbid disorders. The most common psychiatric disorder co-morbid with pediatric bipolar is attention-deficit/hyperactivity disorder (ADHD), with the rates of association ranging from 60 to 90% in prepubertal children and ≤ 60% in adolescents [9,31]. Children with ADHD may be distinguished from children with ADHD co-morbid with bipolar disorder by the absence of elated mood, grandiosity, racing thoughts and hypersexuality and an associated decreased need for sleep [21,32]. Conduct disorder, anxiety and substance abuse are other common co-morbidities associated with PBD [31].

Before treating early-onset bipolar disorder, it is also imperative to thoroughly review the medical history of the child, specifically ruling out medical conditions that could cause mania or depression, exposure to illicit substances or herbal medications or medications causing mood-switching. Furthermore, obtaining a history of familial response to specific psychotropic medications may be helpful.

3. Pharmacotherapeutic options

Although there have been limited placebo-controlled trials involving the use of mood stabilizers and atypical antipsychotics in children with bipolar disorder, the use of these psychotropic agents in this population has increased considerably over the last few years. Data on safety and efficacy of these agents in the pediatric population is based mainly on case reports and small prospective studies, and treatment strategies are often based on data extrapolated from adult studies (**Table 1**). Despite this, lithium and valproic acid remain the mainstay among the traditional mood stabilizers, whereas atypical antipsychotics are rapidly carving out a niche for themselves as potential first-line and adjunctive treatments. Most agents have only been studied for acute mania, but more studies are

Table 1. Summary of completed pharmacotherapy studies in pediatric bipolar disorder.

	Type of study			
	Case report	**Case series**	**Open prospective**	**RCT**
Mood stabilizer				
Lithium	X	X	X	X – positive
Valproate	X	X	X	P
Carbamazepine		X	X	
Lamotrigine	X	X	X	
Topiramate		X		X – negative
Oxcarbazepine	X			X – negative
Gabapentin		X (adjunct)		
Atypical antipsychotic				
Clozapine		X		
Olanzapine		X	X	X – positive
Risperidone		X	X	P
Quetiapine			X	X – positive (adjunct), P (monotherapy)
Ziprasidone	X		X	P
Aripiprazole		X		P

RCT: Randomized controlled trial; P: Study complete, results pending.

being conducted on maintenance strategies and treatments for bipolar depression and co-morbid conditions in PBD.

3.1 Mood stabilizers

3.1.1 Lithium

Lithium is the only mood-stabilizer approved by the US FDA for the treatment of acute mania and bipolar disorder in adolescents or children ≥ 12 years of age. It is one of the few agents to have a double-blind, placebo controlled study supporting its efficacy in this population. In this prospective, placebo-controlled clinical trial of lithium in 25 adolescents suffering from bipolar disorder, Geller *et al.* found that after 6 weeks of treatment, 6 out of 13 subjects receiving lithium had a significant decrease in positive urine toxicology screens in subjects treated with lithium as compared with 1 out of 12 adolescents on placebo [33]. The study also showed a statistically significant decrease in positive urine toxicology screens and a significant improvement in global assessment of functioning (46% in the lithium-treated group versus 8% in the placebo group) [33]. Similarly, anecdotal case reports and open studies have suggested that lithium is efficacious in childhood bipolar disorder [34]. Strober and colleagues, 1990, found that in a study of 37 adolescents suffering from bipolar disorder, the 18-month relapse rate for non-compliant subjects was significantly higher (92%) compared with the rate for those who were compliant with treatment (37.5%) [35].

Lithium is believed to have multiple effects on the second messenger system in the brain, especially working by blocking the activity of inositol polyphosphate 1-phosphatase and inhibiting the adenylyl cyclase system [36]. Recent studies by Manji *et al.* have also shown that lithium might have neurotrophic effects by regulation of cAMP response element binding protein, brain derived neurotrophic factor and MAPKs [37]. It has also been suggested that lithium might indirectly protect against glutamatergic neuronal excitotoxicity [38].

Lithium is rapidly absorbed by the gastrointestinal tract, and has a serum half-life of ~ 18 h in the pediatric population, after which it is excreted by the kidneys. Lithium is also concentrated in the thyroid and may induce hypothyroidism by decreasing the secretion of thyroid hormone. Weller and colleagues suggested that a weight-based dosage of 30 mg/kg/day (three divided dosages) in prepubertal children (6 – 12 years) would result in a therapeutic serum lithium concentration of 0.6 – 1.2 mmol/l [39]. A magnetic resonance spectroscopy study involving Li^7 found children and adolescents to have lower brain-to-serum concentration ratios compared with adults and, thus, children might need higher serum concentrations to maintain therapeutic lithium levels in the brain [40]. However, this study had a small sample size and whether or not children would benefit from higher serum concentrations remains unknown.

The common side effects associated with lithium use in children and adolescents include nausea, abdominal distress, sedation, diarrhea, polyuria, polydipsia, tremor, acne, hypothyroidism and weight gain. Long-term treatment with

lithium may also result in nephrogenic diabetes insipidus resulting from its action on the distal tubules and antidiuretic hormone. Campbell *et al.* reported that these adverse effects may be more commonly observed in younger (5 – 9 years of age), rather than older children [41]. Lithium can also cause cardiac conduction problems, including atrioventricular blocks and irregular sinus rhythms. Hagino *et al.* also reported that younger children may be more likely to develop neurologic adverse effects, including cognitive blunting and headaches, than older children [42]. Lithium can cause seizures, coma and death in toxic doses. Baseline labs including serum electrolytes, renal function tests, thyroid function tests and complete blood count should be drawn along with an electrocardiogram and a pregnancy test before initiating treatment with lithium. Renal functions should be checked every 2 – 3 months in the first 6 months and thereafter every 6 months; thyroid function should be checked every 6 months [43].

It has been reported that ~ 40 – 50% of children and adolescents with bipolar disorder respond acutely to lithium alone [33,44,45]. Rapid discontinuation and non-compliance are associated with a high relapse rate. Clinical factors that predict a poor lithium response in children and adolescents with bipolar disorder include prepubertal onset and the presence of co-morbid ADHD [9]. Co-morbid substance abuse and conduct disorder may also worsen the prognosis. Furthermore, as in adults, it may be less effective in treating mixed mania episodes and rapid cycling, which are commonly seen in adolescents. The presence of a co-morbid personality disorder may also decrease the response rates to lithium [46].

Despite the lack of placebo-controlled data, the authors of this review feel that lithium is a fairly effective mood stabilizer in children and adolescents with classic mania; that is, for episodic presentations, purely manic or depressed, and for children with more euphoric than irritable mania.

3.1.2 Valproic acid (sodium divalproex)

Valproic acid was initially introduced as an antiepileptic medication and has been FDA-approved for treatment of partial seizures and migraines in children and adolescents. The exact mechanism by which valproate works is not unknown, but it appears to potentiate GABAergic functions and may possibly provide neuroprotection against glutamatergic excitotoxicity [47]. It is rapidly absorbed from the gastrointestinal tract, undergoes metabolism in the liver and has a serum half-life varying from 8 to 16 h in the pediatric age group [48].

Although the therapeutic serum valproate concentrations for the pediatric population have not been established, those for adults have been found to be 50 – 125 µg/ml [49]. Usually, children can be started on 250 mg/day and then gradually titrated upwards. Alternatively, they can be started at 15 mg/kg/day in divided or bedtime dosages that can be titrated up to the usual dosage of 15 – 20 mg/kg/day [43]. Liver function tests, complete blood count including platelets and a pregnancy test should be obtained at baseline and thereafter every 6 months.

The potential adverse effects from valproic acid use include nausea, weight gain, sedation, low platelets, hair loss, tremor, hepatic toxicity, pancreatitis, neural tube defects and blood dyscrasias. Valproic acid use has also been associated with the development of polycystic ovarian disease. Isojarvi *et al.*, 1993, reported the association of polycystic ovarian disease in 89% of young females with epilepsy who were on valproic acid as compared with 27% in those not receiving it [50]. Although the exact causative mechanism is unknown, it is hypothesized that obesity develops secondary to valproic acid use leading to elevated insulin and androgen levels resulting in menstrual abnormalities, acne and hirsutism.

In the US, divalproex is the widely used form of valproic acid due to its greater tolerability. Divalproex (including the extended-release form) has been approved by the US FDA for the treatment of acute mania in adults with bipolar disorder. Although divalproex has been used widely for managing PBD, there are still no placebo-controlled studies of divalproex published in this population. Thus, the evidence for its efficacy largely consists of open studies and case series [51-53]. These open studies show response rates of pediatric mania to divalproex in the range of 53 – 82%.

Valproate appears to be an effective agent for treating manic symptoms in children and adolescents with a variety of bipolar spectrum disorders, including BD-NOS. Its broad-spectrum action is reflected by its use in seizure disorders, migraine and aggression. It may also prove to be effective as a preventative intervention early in the course of bipolar disorder development [54], given early clinical data and *in vitro* neuroprotective qualities [55].

3.1.3 Carbamazepine

Carbamazepine was initially launched as an antiepileptic medication and has been FDA-approved for trigeminal neuralgia and for generalized and partial seizures in adults and children > 6 years of age. It is believed to involve inhibition of cAMP formation and possibly has a role in cell membrane stabilization [56]. Carbamazepine is readily absorbed and thereafter undergoes hepatic metabolism by CYP3A4 to carbamazepine 10,11-epoxide, an active metabolite. It can also induce its own metabolism using the same hepatic pathway, decreasing its own serum levels after 3 – 5 weeks of treatment. Therapeutic serum carbamazepine concentrations, extrapolated from the epilepsy and adult bipolar literature, are 4 – 12 µg/ml. The usual starting dose in the prepubertal population is 100 mg b.i.d., with gradual upward titration to a maximum of 10 – 20 mg/kg/day. Adolescents usually achieve therapeutic serum levels at 400 – 1400 mg/day in two or three divided doses a day [57]. When using carbamazepine in combination with other mood stabilizers, it is also important to note that carbamazepine can decrease the levels of lamotrigine and decrease lithium clearance, whereas valproic acid can increase carbamazepine levels [58,59].

The adverse effects from carbamazepine use include sedation, dizziness, ataxia and blurred vision. Carbamazepine has also

been associated with Stevens-Johnson syndrome, hyponatremia, aplastic anemia and agranulocytosis. Apart from baseline complete blood counts, it is good practice to educate the subject regarding the possibility of such a hematological event, and thus to carefully monitor for fever, sore throat and easy bruising.

Again, the data for carbamazepine use in PBD is limited to case reports indicative of successful use either as monotherapy [60] or as an adjunct to lithium [61]. These reports also indicate that carbamazepine might be effective in adolescents with PBD who do not respond to lithium.

Kowatch *et al.*, 2000, compared the efficacy of these three mood stabilizers in an open study involving 42 out-patients with a mean age of 11.4 years (20 with bipolar I disorder and 22 with bipolar II disorder) [62]. These subjects were randomly assigned to 6 weeks of open treatment with either lithium, divalproex or carbamazepine. Although there were no significant differences in the efficacy of the three mood stabilizers, the researchers concluded that the effect size was 1.63 for divalproex, 1.06 for lithium and 1.00 for carbamazepine, with the response rates being: divalproex 53%; lithium 38%; and carbamazepine 38%. All three mood stabilizers were well tolerated and no serious adverse effects were seen [62]. No other similar studies have compared the efficacy of these mood stabilizers in PBD.

It is likely that carbamazepine is underused in child psychiatry due to adverse effects and CYP450 metabolism concerns. Further controlled studies in PBD would help clinicians place this agent in the proper category for use.

3.1.4 *Newer anticonvulsants*

Newer antiepileptic medications, including oxcarbazepine, lamotrigine, gabapentin and topiramate, have been used as adjunctive mood stabilizers for PBD. As most of them have not been studied as a primary mood stabilizer for PBD, the clinically significant features of each of them are discussed here.

Oxcarbazepine is a 10-keto analog of carbamazepine that appears to have a reduced risk for leukopenia, rashes, interactions and autoinduction compared with carbamazepine. Teitelbaum and colleagues reported a case of remission in a child with unstable bipolar disorder by using adjunctive oxcarbazepine [63]. In a recent study, Macmillan *et al.*, 2006, reviewed medical records and compared valproic acid with oxcarbazepine for treating aggression in youths with bipolar disorder. These researchers found that a greater reduction in Clinical Global Impressions-Severity (CGI-S) and CGI-S specific to aggression scores occurred with valproic acid as compared with oxcarbazepine at 4 months of study. Thus, oxcarbazepine appeared less effective than valproic acid for PBD with aggression in this study [64]. In a recent multi-center trial examining the efficacy and safety of oxcarbazepine in PBD involving 116 out-patients with bipolar I disorder, manic or mixed, Wagner *et al.* reported that oxcarbazepine (mean dose = 1515 mg/day) was not more effective than placebo in reducing manic symptoms. At least 5% of the patients in the oxcarbazepine group developed dizziness, nausea, somnolence, diplopia, fatigue or rash, with an incidence at least twice that of the placebo group [65]. Children < 12 years of age were found to respond better to oxcarbazepine than placebo (41 versus 17% response rate, respectively). Nonetheless, there is little to no evidence supporting the use of oxcarbazepine in PBD at present.

Lamotrigine has also been studied as an adjunctive treatment for PBD, especially bipolar depression, in a few case reports. Although lamotrigine holds promise, especially for the depressed phase, its use in children has been limited in the past because of potentially lethal Stevens-Johnson syndrome and toxic epidermal necrolysis [66]. More recent data, following dosage guidelines that recommended slower dose titration, suggest a much lower rate of rash, especially serious rash, in pediatric patients [67]. For adolescents and adults with bipolar disorder not taking valproate or carbamazepine concurrently, the initial recommended dosage is 25 mg/day (weeks 1 and 2), which is increased to 50 mg/day (weeks 3 and 4), then 100 mg/day (week 5) and then 200 mg/day from week 6 [68]. A recent 8-week open trial prospectively studied the efficacy of lamotrigine as adjunctive or monotherapy in 20 adolescents with bipolar disorder who were experiencing a depressive episode. A large majority (84%) of these adolescents responded to the treatment and 58% achieved remission at week 8. Mean dose at week 8 was 132 mg/day, and there was no significant weight change, rash or other adverse effects during the trial [69]. Thus, lamotrigine may prove to be an important agent in the management of bipolar depression in adolescents.

Gabapentin was initially used as an adjunct for treating bipolar disorder in adults; however, later studies found that it was no more effective than placebo for this purpose [70]. There is no controlled data on the efficacy of gabapentin in PBD. Some case studies have suggested its role in treating children with PBD with co-morbid anxiety disorders [71,72]. Thus, although most likely not effective for acute pediatric mania in monotherapy, gabapentin may be useful adjunctly, especially for the treatment of co-morbid anxiety.

Topiramate has also been studied in open studies as an adjunctive treatment for PBD. DelBello *et al.* reviewed the out-patient charts of 26 youths with PBD I or II who were on topiramate. It was found that topiramate was effective as an adjunct in PBD [73]. Moreover, topiramate has been found to cause weight loss through appetite suppression and may thus be beneficial in youths who have gained weight with antipsychotic or mood stabilizer use. A double-blind, placebo-controlled study to assess the efficacy of topiramate monotherapy for acute mania in PBD was discontinued early when adult mania trials with topiramate failed to show efficacy. This study involving 56 children and adolescents (6 – 17 years of age) had inconclusive results, although topiramate was well tolerated [74]. Adequately powered controlled trials are needed to determine whether or not topiramate has efficacy in reducing symptoms of PBD.

3.2 Atypical antipsychotics

Atypical antipsychotics have been found to be efficacious for the treatment of schizophrenia and bipolar disorder in adults, but the knowledge about these second-generation agents in PBD is limited primarily to open-label studies and case reports. Most of these studies have examined the efficacy of risperidone, olanzapine, clozapine or quetiapine for childhood mania. Quetiapine was the first atypical antipsychotic to be studied in a double-blind placebo-controlled trial for the treatment of adolescent mania. This study involved 30 adolescents diagnosed with PBD I (mixed or manic) who initially received divalproex (20 mg/kg) and were then randomized to 6 weeks of adjunct treatment with quetiapine (≤ 450 mg/day) or with placebo. The combination of quetiapine plus valproate led to a significant reduction in YMRS scores as compared with valproate plus placebo [75].

In a recent trial to determine the comparative efficacy of quetiapine and divalproex for the treatment of adolescent mania, Delbello *et al.* reported that quetiapine was at least as effective as divalproex in the treatment of acute manic symptoms. In this study, 50 adolescents (12 – 18 years of age) with bipolar I disorder, manic or mixed episode, were randomized to quetiapine (400 – 600 mg/day) or divalproex (serum level 80 – 120 µg/ml) for 28 days, with change in YMRS scores used as the primary efficacy measure. Furthermore, response and remission rates were found to be significantly greater in the quetiapine group, suggesting that quetiapine may be useful as monotherapy for the treatment of adolescents with manic or mixed episodes [76].

Trials are ongoing to study the efficacy for most of the atypical antipsychotics including risperidone, olanzapine and quetiapine in PBD. The common adverse effects seen with almost all atypical antipsychotics include sedation, hypotension, weight gain, dizziness and dry mouth.

In an open-label study with seven adolescents in the manic phase, Soutullo *et al.*, reported that 71% had a moderate or marked improvement with olanzapine [77]. In an 8-week, open-label, prospective study of effectiveness and tolerability of olanzapine monotherapy (2.5 – 20 mg/day) involving 23 youths suffering from PBD (mania, mixed or hypomania), olanzapine treatment was associated with a significant improvement in mean YMRS score and was well tolerated [78]. Another prospective open study to evaluate short-term safety and efficacy in treatment of preschoolers with bipolar disorder with olanzapine or risperidone suggested that treatment with atypical antipsychotics led to a rapid reduction of symptoms of mania in preschool children with PBD [79]. Finally, olanzapine has been studied in monotherapy in a placebo-controlled, 3-week study in children and adolescents with acute mania [80]. A total of 107 subjects were randomized to olanzapine versus 57 to placebo, beginning at 2.5 – 5.0 mg/day and titrating up to 10 – 20 mg/day. Subjects taking olanzapine demonstrated greater reduction in mania symptoms (change in YMRS score = -17.7 versus -10.0) and higher response rates (48 versus 18.5%) compared with those taking placebo. Remission was also higher in the olanzapine group (35 versus 11%). Subjects taking olanzapine compared with placebo also had a greater weight gain (3.7 versus 0.3 kg), prolactin increase (15.4 versus 2.7) and cholesterol increase (14.3 versus 1.2) by the end of the study.

Risperidone, although widely used, has limited studies in PBD [81]. In a prospective open-label trial, Biederman *et al.* treated 30 youths with PBD with risperidone monotherapy for 8 weeks and reported a significant improvement in manic symptoms in 70% of subjects, using response criteria of a 30% decrease in manic symptoms, or clinician rated moderate or marked improvement. Treatment with risperidone treatment was associated with orthostatic hypotension, weight gain, sedation, prolactin elevation and development of extrapyramidal symptoms [82]. Risperidone and olanzapine were compared in an open study of the treatment of preschool mania. Subjects were 4 – 6 years of age and response rates (using the same criteria above) were not significantly different for olanzapine and risperidone monotherapy (53 and 69%, respectively) [79].

Clozapine was found to show improvement in a series of five children and adolescents with mixed mania who had not previously shown any response with other antipsychotics. Another study by Masi *et al.*, 2002, showed similar efficacy in 10 adolescents in an in-patient setting [83]. The side effects from clozapine include sedation, weight gain and increased salivation, along with potentially lethal agranulocytosis, seizures and myocarditis [84,85]. Clozapine is usually recommended only after inadequate response to at least two other antipsychotics at optimal dosages.

There are only anecdotal reports of efficacy of ziprasidone in PBD. Barnett, 2004, reported a significant improvement of symptoms in four children with bipolar-like disorders who were switched from various mood stabilizers to ziprasidone [86]. Similarly, a retrospective case report found aripiprazole mono- or adjunct therapy to be associated with improvement in manic symptoms with no serious adverse effects [87]. In adults, both these agents are associated with a somewhat lower risk of weight gain and possibly metabolic syndrome. However, preliminary data suggest that children and adolescents taking these medications still tend to gain weight beyond expected developmental trajectories [88]. Randomized placebo-controlled trials in pediatric mania are being carried out with both these atypical agents, which will provide sorely needed efficacy and safety data for these agents.

Recent research studying adverse events with atypical antipsychotics, especially olanzapine (and clozapine) have focused on significant metabolic problems resulting from a notable weight gain. These metabolic side effects have included excessive weight gain, Type II diabetes mellitus or hyperglycemia and hyperlipidemia [89]. The American Diabetes Association has published a protocol for adults on these medications to be monitored with an assessment including baseline and repeat measurement of weight, body mass index, blood pressure, blood sugar and lipid profile at stipulated intervals [90].

Although these guidelines recommend that the patient should be switched to an alternative agent in case of a > 5% weight gain, this threshold might not be appropriate for the pediatric population. Recent data suggests that children are particularly susceptible to weight gain, and thus potentially metabolic complications, when treated with all atypical antipsychotics [88].

Thus, these authors feel that at present, olanzapine may be the most effective agent for pediatric mania, but may also have the largest potential for weight gain. Quetiapine also appears effective and has an intermediate weight-gain profile. Risperidone may be helpful, and the efficacy of aripiprazole and ziprasidone are unclear at present. Clozapine would appear effective for pediatric mania, but should be considered a last resort agent due to the potential for serious adverse effects. Fortunately, placebo-controlled data for these agents in PBD should be forthcoming soon (with the exception of clozapine). Empirical data also suggests that these agents are especially useful in combination with traditional mood stabilizers [75].

3.3 Non-pharmacologic interventions

Considering the effects that PBD can have on the quality of life of both individuals and their families, psychosocial interventions are a critical component in treatment. Again, there are few preliminary studies that target psychosocial treatment for PBD, and almost all of these involve implementation of therapy when the youth is stable enough to receive psychoeducation. Fristad *et al.* used multiple family group treatment for children aged 8 – 12 years that involved psychoeducation including education regarding the role of medications and coping mechanisms [91]. Pavuluri *et al.* recently designed a child- and family-focussed cognitive–behavioral therapy specifically for PBD. This method integrates cognitive–behavioral therapy and interpersonal principles of psychotherapy, helps parents become aware of their own cognitions and learn new skills to help serve as coaches for their children. Although the trial is limited by an open design, preliminary data indicates a good response to this method [92]. Family focussed therapy for adolescents with bipolar disorder is another promising intervention, with positive open data [93] and a controlled multisite study underway.

Some recent open-label studies have also described supplementation with a broad-based nutrient formulae containing vitamins, minerals and sometimes essential fatty acids. Kaplan *et al.* in an open-label study, explored the potential efficacy of a nutrient supplement in 11 children with mood and behavioral problems using the Child Behavior Checklist, Youth Outcome Questionnaire and YMRS at entry and at 8 weeks of treatment [94]. These researchers described relatively large effect sizes for all outcome measures and recommended that formal clinical trials of broad nutritional supplementation are needed in children with these psychiatric symptoms [94]. In another open-label study, Kaplan *et al.* describe adult subjects with bipolar disorder showing improvement in their symptoms using a chelated mineral supplement over a 6-month period. Although these open-label studies suggest that nutritional supplements may be helpful in improving symptoms of mood disorders or decreasing psychotropic medication use in this population, randomized, placebo-controlled trials are needed to demonstrate the safety and efficacy of such supplementation [95].

Electroconvulsive therapy (ECT) is an effective treatment for mania in adults, but is only offered for patients who do not respond to standard medications. ECT is also considered the treatment of choice for bipolar disorder in pregnancy, catatonia and in some cases of neuroleptic malignant syndrome. The research data regarding ECT in children and adolescents is very limited. The present practice involves considering ECT only for adolescents with well-characterized bipolar I disorder that have severe episodes of mania or depression that are unresponsive to standard psychotropic medications [96]. Given the present evidence base, ECT should not be considered for patients with BD-NOS or atypical presentations of juvenile mania.

4. Treatment strategies

It is becoming evident that children and adolescents with bipolar disorder require a multidisciplinary treatment approach consisting of pharmacotherapy, psychotherapy and educational interventions [97]. However, most non-pharmacologic interventions are at present considered as adjunctive therapy to medications. The authors concentrate on pharmacotherapeutic interventions for the purposes of this review. Regarding pharmacotherapy, treatment recommendations have been based primarily on open prospective studies, a few controlled studies, extrapolation from the adult literature, case reports and expert opinion. The overall recommended treatment strategy for children with acute mania would be to use a traditional mood stabilizer (lithium or valproate) or an atypical antipsychotic as the primary treatment, with other psychotropic medications serving to aid in mood stabilization and/or to treat co-morbid conditions. Most experts in the field agree that when treating PBD, the initial goal is to stabilize the mood and then treat the associated co-morbidities [98]. The target goals of treatment should include a reduction in acute symptoms, prevention of relapse, reduction in long-term morbidity and promotion of normal development. No single medication has been approved by the FDA for the treatment of all phases of bipolar disorder; thus, the course of pharmacologic treatment would likely involve a combination of psychotropic agents.

The choice of medications is usually based on a combination of the following factors:

- subtype of bipolar disorder
- the phase of illness
- efficacy of an agent
- presence of psychotic symptoms
- adverse effect profile, including need for blood draws
- previous history of response to an agent
- family history of response to an agent
- co-morbidity

4.1 Subtype of bipolar disorder

There is some indication that certain medications may be more effective for certain subtypes of PBD. For example, lithium may be particularly effective for children and adolescents presenting with classic euphoric mania without psychotic symptoms, whereas valproate may be a better choice for a child with more chronic irritability and/or ultra-rapid cycling of mood [4,43]. Stringent studies on this topic, however, have not been performed in PBD. There are some indications, however, that lithium may be less effective in children with co-morbid personality disorders or in children who have a prepubertal onset of any psychiatric disorder (including bipolar disorder) [34].

4.2 Phase of illness

Most pharmacotherapy studies in PBD have been conducted for the manic phase of PBD, and thus a mood stabilizer or atypical antipsychotic as first-line treatment usually refers to treating manic symptoms. The treatment of the bipolar depressed phase in the pediatric age group has limited data, although lamotrigine and lithium may be promising options [69,99]. Quetiapine deserves further study in adolescent bipolar depression, given positive data in adults [100]; a small placebo-controlled study in adolescents is underway. The role of antidepressants in pediatric bipolar depression is relatively unclear. A small retrospective study indicated that such patients showed a significant improvement in symptoms by using selective serotonin re-uptake inhibitors, but were also at greater risk for switching to mania [101]. Other larger retrospective studies have indicated that children and adolescents with bipolar disorder may be particularly prone to antidepressant induced mania (AIM), with ≤ 50% of one sample having experienced AIM at one time, regardless of concurrent treatment with a mood stabilizer or antipsychotic [102]. Therefore, antidepressants in this population to treat bipolar depression, or even co-morbid anxiety, should be used cautiously, if at all, until more rigorous studies are conducted.

Maintenance treatment has also been understudied in this population. Present recommendations include maintaining the child on the medication regimen that worked to achieve stability for at least 18 months before considering tapering off medications. Clearly, if symptoms remain or there is a history of suicide or dangerous behavior during mood episodes, children with PBD may need to continue medications indefinitely [98].

4.3 Efficacy of an agent

Although there are limited placebo-controlled trials in PBD, numerous open-label trials and case studies have been carried out using a variety of psychotropic agents as discussed previously (**Table 2**). The only positive placebo-controlled studies for pediatric mania have involved lithium, quetiapine and olanzapine. The evidence base with newer antiepileptic agents is still lacking, although lamotrigine appears to be a promising agent for the depressed phase [69]. Among the atypical antipsychotics, quetiapine is perhaps the best studied in PBD, with studies suggesting that quetiapine is at least as effective as divalproex in the treatment of acute manic symptoms [76]. Olanzapine also appears to have good efficacy in pediatric mania, with its use only being limited by tolerability and adverse effect profile (see Section 4.4).

4.4 Adverse effects, including the need for blood draws

The need for blood draws and associated adverse events, including weight gain, hypothyroidism, acne and long-term renal problems, are all potential problems that a child may have to deal with when taking lithium. Similarly, blood draws for serum levels are also needed with valproic acid and carbamazepine. The common adverse effects with these two agents have already been discussed. Although some children may have difficulty with the phlebotomy process, relaxation techniques and the use of an eutectic mixture of lidocaine and prilocaine cream (lidocaine 2.5% and prilocaine 2.5%) may decrease these concerns. Atypical antipsychotics, because of ease of administration and no need for repeated blood draws, may at first seem preferable treatments in children with bipolar disorder. However, the association of weight gain and metabolic syndrome with these medications warrants a careful clinical monitoring of youths who have been prescribed these medications. Thus, children prescribed antipsychotics also require regular monitoring of fasting glucose, along with baseline and follow-up lipid profiles, thus diminishing the advantage of using atypicals over traditional mood stabilizers. Therefore, primary considerations in this category should be based on individual concerns regarding adverse effects. For example, if an adolescent female already has signs of polycystic ovarian syndrome, divalproex would no longer be the first choice in treatment. Similarly, in children with diabetes and bipolar disorder, it would be wise to avoid atypical antipsychotics as first-line treatment.

4.5 Psychotic symptoms

In children who present with PBD with associated psychotic symptoms, initial treatment should be a combination of a traditional mood stabilizer (lithium, divalproex or carbamazepine) and an atypical antipsychotic [98]. DelBello *et al.* compared the use of a combination of quetiapine (titrated ≤ 450 mg/day) and valproic acid versus valproate monotherapy for adolescent mania (47% of subjects had psychosis) and found that the combination resulted in a greater reduction of symptoms of mania [76]. Lower rates of relapse for adolescents with acute psychotic mania were reported when antipsychotic medication was maintained for at least 4 weeks in combination with lithium [103]. Similarly, in an open-label trial, Pavuluri *et al.* compared the efficacy of risperidone and lithium versus risperidone and sodium valproate in an open trial studying 37 youths suffering from manic and mixed episodes. They reported that risperidone when combined with either lithium or valproate appeared to be equally safe and efficacious in mixed or manic episodes of PBD. Furthermore, the severity of psychosis appeared to decrease in both groups over the 6-month study [104].

Table 2. Summary of open prospective and randomized controlled trials in pediatric bipolar disorder.

	Type of study	First author, year	Number	Age range (years)	Bipolar disorder type	Phase studied	Duration (weeks)	Response criteria	Outcome	Comments
Mood stabilizer										
Lithium										
	Open	Strober *et al.* (1990) [35]	37	13 – 17	I	Maintenance	18 months	Relapse considered full manic or depressive episode	92% of Li discontinuers (12/13) relapsed, versus 38% of subjects remaining on Li	6 Li continuers with adjunctive medications
	DBPCRT	Geller *et al.* (1998)	25	12 – 18	I, II, MDD	Manic, depressed with bipolar disorder predictors	6	CGAS ≥ 65	Positive – 6/13 (46%) responders, versus 1/12 on PBO	Primary outcome studied was substance abuse, decreased in Li group
	Open	Kafantaris *et al.* (2003) [34]	100	12 – 18	I	Manic, mixed	4	33% decrease in YMRS and 1 or 2 on CGI-I	63 (63%) responders	26 remitters (YMRS < 7), subjects with psychosis received adjunct antipsychotics
	DBPCRT	Kafantaris (2004)	40	12 – 18	I	Maintenance (responders from 2003 open trial)	2	Relapse criteria: 4 or 5 on CGI-I	Relapsed: 10/19 (53%) on Li versus 13/21 (62%) on PBO (no significant difference)	2 weeks may have been too short to detect differences
	Open	Patel *et al.* (2006) [99]	27	12 – 18	I	Depressed	6	50% decrease in CDRS	13/27 (48%) responders	8 (30%) remitters
Valproate										
	Open	Papatheorodou (1995)	15	12 – 20	I	Manic	7	50% reduction in MMRS	12/15 (80%) responders	
	Open	Wagner *et al.* (2002) [51]	36	7 – 19	I, II	Manic, hypomanic, mixed	2 – 8	50% reduction in YMRS	22/36 (61%) responders	23 discontinued study prematurely
	Open	Scheffer *et al.* (2005) [52]	40	6 – 17	I, II	Manic, hypomanic	8	50% reduction in YMRS	32/40 (80%) responders	Lead into DBPC RT of adjunctive stimulant

CARB: Carbamazepine; CDRS: Childrens depression rating scale; CGAS: Children's Global Assessment Scale; CGI-I: Clinical global impression – improvement; CGI-S Clinical global impression – severity; DB: Double-blind; DBPC: Double-blind, placebo-controlled; DBPCRT: Double-blind, placebo-controlled, randomized trial; DBRCT: Double-blind, randomized controlled trial; DVPX: Divalproex; HAM-D: Hamilton depression rating scale; Li: Lithium; MDD: Major depressive disorder; MMRS: Modified mania rating scale; NOS: Not otherwise specified; OLZ: Olanzapine; PBO: Placebo; PCRT: Placebo-controlled, randomized trial; prn: As needed; QUET: Quetiapine; RT: Randomized trial; RCT: Randomized controlled trial; RISP: Risperidone; SB: Single-blind; SBRCT: Single blind, randomized controlled trial; SSRIs: Selective serotonin reuptake inhibitors; YMRS: Young mania rating scale.

Table 2. Summary of open prospective and randomized controlled trials in pediatric bipolar disorder (continued).

	Type of study	First author, year	Number	Age range (years)	Bipolar disorder type	Phase studied	Duration (weeks)	Response criteria	Outcome	Comments
Valproate plus Lithium	Open	Findling *et al.* (2003) [44]	90	5 – 17	I, II	Any	≤ 20	CDRS ≤ 40, YMRS ≤ 12.5, and CGAS ≥ 51 for 4 consecutive weeks	42 (47%) in remission	Some subjects on concomitant stimulants, antipsychotics, SSRIs
Valproate vs Lithium	DBRCT	Findling *et al.* (2005) [107]	60	5 – 17	I, II	Maintenance (from subjects in remission from 2003 open trial)	18 months	Premature discontinuation due to relapse of mood symptoms	No difference between lithium and DVPX groups	Median survival 114 versus 111 days in DVPX versus Li groups
Li vs DVPX vs CARB	Open RCT	Kowatch *et al.* (2000) [62]	42	6 – 18	I, II	Manic, hypomanic, mixed	6 – 8	50% decrease in YMRS	Response rate: Li 38%, DVPX 53%, CARB 38%	No significant difference between groups
Lamotrigine										
	Open, adjunctive to DVPX	Kusumaker (1997)	22 (7 adolescents)	Mean age 25 +/- 12	Unclear	Depression or rapid cycling	6	50% decrease in HAM-D	72% response	63% remitted, no rash
	Open	Chang *et al.* (2006) [54]	20	12 – 17	I,II, NOS	Depression	8	1 or 2 on CGI-I or 50% reduction in CDRS	16 (84%) by CGI-I, 12 (63%) by CDRS	7 subjects with adjunct meds; 58% remitted, no serious rash
Topiramate										
	DBPCRT	DelBello *et al.* (2005) [74]	56	6 – 17	I	Mania, mixed	4	Overall reduction in YMRS	Negative – no difference between groups	Weight loss greater in topiramate group
Oxcarbazepine										
	DBPCRT	Wagner *et al.* (2006) [65]	116	7 – 18	I	Manic, mixed	7	Overall decrease in YMRS; 50% reduction in YMRS	No difference between groups; 42% response in active versus 26% placebo	7 – 12 year olds with significantly higher response rate (41 versus 17%)

CARB: Carbamazepine; CDRS: Childrens depression rating scale; CGAS: Children's Global Assessment Scale; CGI-I: Clinical global impression – improvement; CGI-S: Clinical global impression – severity; DB: Double-blind; DBPC: Double-blind, placebo-controlled; DBPCRT: Double-blind, placebo-controlled, randomized trial; DBRCT: Double-blind, randomized controlled trial; DVPX: Divalproex; HAM-D: Hamilton depression rating scale; Li: Lithium; MDD: Major depressive disorder; MMRS: Modified mania rating scale; NOS: Not otherwise specified; OLZ: Olanzapine; PBO: Placebo; PCRT: Placebo-controlled, randomized trial; prn: As needed; QUET: Quetiapine; RT: Randomized trial; RCT: Randomized controlled trial; RISP: Risperidone; SB: Single-blind; SBRCT: Single blind, randomized controlled trial; SSRIs: Selective serotonin reuptake inhibitors; YMRS: Young mania rating scale.

Table 2. Summary of open prospective and randomized controlled trials in pediatric bipolar disorder (continued).

	Type of study	First author, year	Number	Age range (years)	Bipolar disorder type	Phase studied	Duration (weeks)	Response criteria	Outcome	Comments
Atypical antipsychotic										
Olanzapine										
	Open	Frazier *et al.* (2001) [78]	23	5 – 14	I, II	Manic, mixed, hypomanic	8	1 = 30% decrease in YMRS and CGI-S ≤ 3 or 2 = 50% decrease in YMRS	YMRS decreased 19.0, 1 = 61% reponse, 2 = 74% response	Weight gain = 5.0 kg
	DBPCRT	Tohen *et al.* (2005) [80]	159 (2:1, OLZ:PBO)	10 – 17	I	Manic, mixed	3	50% decrease in YMRS	OLZ = 48%, PBO = 18.5%	42% gained at least 7% of body weight, remitters = 35 versus 11%
Risperidone										
	Open	Biederman (2005)	30	6 – 17	I, II	Manic, hypomanic, mixed	8	1 or 2 on CGI-I	70% response	2.1 kg weight gain
Risperidone versus Olanzapine	Open	Biederman (2005)	31	4 – 6	I, II, NOS	Manic, hypomanic or mixed symptoms	8	30% decrease in YMRS and CGI-I = 1 or 2	Risp = 69% versus OLZ = 53% no significant difference	Increases in serum prolactin and weight in both groups; stimulants allowed
Risperidone plus lithium versus plus DVPX	Open	Pavuluri (2004)	30	5 – 18	I	Manic, mixed	6 months	YMRS change, 50% decrease in YMRS	Effect size for DVPX = 4.36, Li = 2.83. Response was DVPX = 80%, Li = 82.4%	Stimulants and other prn's allowed
Quetiapine										
	DBRCT, Adjunct to VPA	DelBello (2002)	30	12 – 18	I	Manic	6	50% decrease in YMRS	87% QUET, 53% PBO	Greater sedation in combined group

CARB: Carbamazepine; CDRS: Childrens depression rating scale; CGAS: Children's Global Assessment Scale; CGI-I: Clinical global impression – improvement; CGI-S Clinical global impression – severity; DB: Double-blind; DBPC: Double-blind, placebo-controlled; DBPCRT: Double-blind, placebo-controlled, randomized trial; DBRCT: Double-blind, randomized controlled trial; DVPX: Divalproex; HAM-D: Hamilton depression rating scale; Li: Lithium; MDD: Major depressive disorder; MMRS: Modified mania rating scale; NOS: Not otherwise specified; OLZ: Olanzapine; PBO: Placebo; PCRT: Placebo-controlled, randomized trial; prn: As needed; QUET: Quetiapine; RT: Randomized trial; RCT: Randomized controlled trial; RISP: Risperidone; SB: Single-blind; SBRCT: Single blind, randomized controlled trial; SSRIs: Selective serotonin reuptake inhibitors; YMRS: Young mania rating scale.

Table 2. Summary of open prospective and randomized controlled trials in pediatric bipolar disorder (continued).

	Type of study	First author, year	Number	Age range (years)	Bipolar disorder type	Phase studied	Duration (weeks)	Response criteria	Outcome	Comments
Quetiapine versus DVPX	SBRCT	DelBello (2006)	50	12 – 18	I	Manic, mixed	4	Change in YMRS	-23 QUET, -19 DVPX	No significant difference, but remission QUET 60%, DVPX 28%
Ziprasidone										
	Open	Versavel (2005)	46	10 – 17	I	Manic, mixed	3	Change in YMRS	-14.9 in low dose group, -11.1 in high dose group	40 mg/day or 80 mg/day (dose finding study)

CARB: Carbamazepine; CDRS: Childrens depression rating scale; CGAS: Children's Global Assessment Scale; CGI-I: Clinical global impression – improvement; CGI-S Clinical global impression – severity; DB: Double-blind; DBPC: Double-blind, placebo-controlled; DBPCRT: Double-blind, placebo-controlled, randomized trial; DBRCT: Double-blind, randomized controlled trial; DVPX: Divalproex; HAM-D: Hamilton depression rating scale; Li: Lithium; MDD: Major depressive disorder; MMRS: Modified mania rating scale; NOS: Not otherwise specified; OLZ: Olanzapine; PBO: Placebo; PCRT: Placebo-controlled, randomized trial; prn: As needed; QUET: Quetiapine; RT: Randomized trial; RCT: Randomized controlled trial; RISP: Risperidone; SB: Single-blind; SBRCT: Single blind, randomized controlled trial; SSRIs: Selective serotonin reuptake inhibitors; YMRS: Young mania rating scale.

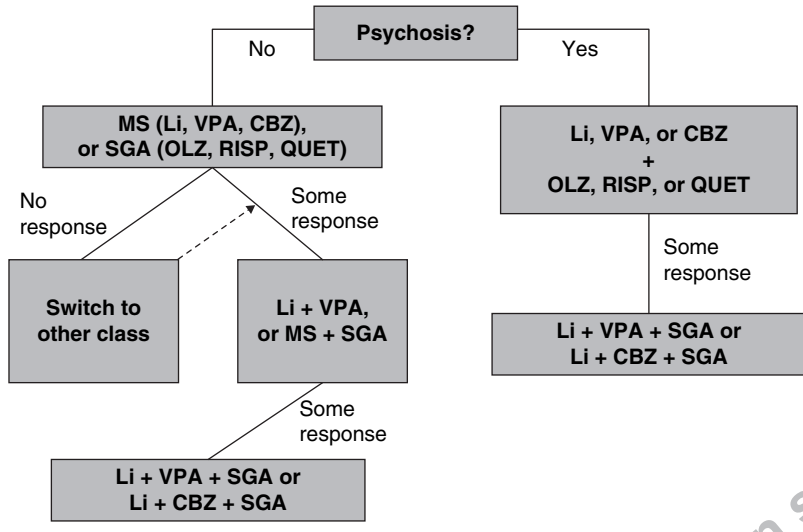

Figure 1. Treatment of acute mania in pediatric bipolar disorder.
Based on KOWATCH RA *et al.*: *J. Am. Acad. Child Adolesc. Psychiatry* (2005) **44**(3):213-235 [98].
CBZ: Carbamazepine; Li: Lithium; MS: Mood stabilizer; OLZ: Olanzapine; QUET: Quetiapine; RISP: Risperidone; SGA: Second generation antipsychotic; VPA: Valproate.

4.6 Previous and family history of response

In case of a previous or family history of a good response to a psychotropic medication, it is usually good clinical practice to initiate treatment with the same agent. However, the clinician must also take into consideration the other factors listed here when making such a decision. A past trial with an agent should be carefully examined to ensure that the medication dosage and the treatment duration are appropriate before ruling out its reuse. Furthermore, it is possible that agents tried at a much younger age could have improved efficacy at an older age. In addition, a good response of a relative to lithium certainly does not assure the same success in the child with PBD.

4.7 Co-morbidity

Another common clinical scenario involves the presence of co-morbid psychiatric disorders with PBD. Co-morbid disruptive behavioral disorders and ADHD have been found to be associated with a poorer response to treatment. Most clinicians agree that stimulant medications may be helpful for addressing ADHD symptoms once the mood symptoms of the patient are adequately controlled on a mood stabilizer regimen. Scheffer *et al.* conducted a randomized controlled trial of 40 children and adolescents with PBD and co-morbid ADHD and found that the use of low-dose mixed amfetamine salts was safe and effective for the treatment of co-morbid ADHD once the mood symptoms of the child were stabilized with divalproex [52]. Similarly, Galanter *et al.* analyzed data from a 1-month methylphenidate titration trial of the Multimodal Treatment Study of Children with ADHD and suggested that children with ADHD and manic symptoms respond to methylphenidate during the first month of treatment and that these children are not more likely to have an adverse response to methylphenidate [105].

Other co-morbid conditions such as anxiety, substance use and conduct disorder should also be considered when choosing medications. For example, olanzapine and quetiapine may reduce co-morbid anxiety in adults with bipolar disorder [106], and thus might be the first choice in a child with PBD and a co-morbid anxiety disorder.

Based mostly on 4.3 and 4.4 Kowatch *et al.*, 2005, in their expert consensus guidelines on the subject, described two algorithms for acute treatment of PBD, type I (manic or mixed type), depending on whether the child presents with or without features of psychosis. In patients without psychosis, they suggested initiating treatment with monotherapy involving traditional mood stabilizers (lithium, valproic acid or carbamazepine) or atypical antipsychotics (olanzapine, quetiapine or risperidone), with the majority of the consensus panel opting for lithium or valproic acid as their first choice [96]. Aripiprazole and ziprasidone were not yet recommended as first-line treatment due to their relative lack of efficacy data in this population. In children with PBD with psychotic features, they recommend starting one of the traditional mood stabilizers concurrently with an atypical antipsychotic. **Figures 1** and **2** show the recommendations made by this consensus panel in a concise form. An optimal trial with a pharmacologic agent should last at least 6 – 8 weeks at optimal dosages of the medication before the clinician switches or augments the agent.

Although there is little research regarding the necessary duration of treatment in PBD, most researchers and clinicians would agree that the treatment needed to stabilize acute mania should be maintained for 12 – 24 months.

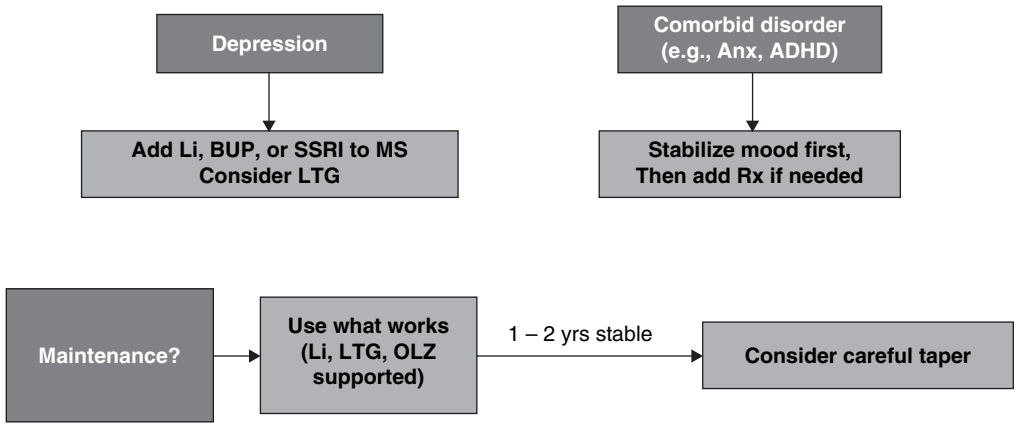

Figure 2. Treatment issues in pediatric bipolar disorder.

Based on KOWATCH RA *et al.*: *J. Am. Acad. Child Adolesc. Psychiatry* (2005) **44**(3):213-235 [98].

Anx: Anxiety; BUP: Bupropion; Li : Lithium; LTG: Lamotrigine; MS: Mood stabilizer; OLZ: Olanzapine; Rx: Medication; SSRI: Selective serotonin reuptake inhibitor.

Maintenance therapy is often needed for youths with bipolar disorder, with some youths requiring lifelong therapy. This consensus panel led by Kowatch *et al.* noted that whereas lithium, divalproex and carbamazepine have been the agents most commonly used to treat children and adolescents with PBD, present research in adults supports the efficacy of lithium, lamotrigine and olanzapine as maintenance treatments [96]. Due to the relative paucity of maintenance studies in the pediatric population, the consensus group recommended that maintenance treatment studies be a high priority, especially as PBD is a chronic condition with a high risk of relapse. In a recent study, Findling *et al.* tried to determine whether divalproex was superior to lithium in maintenance monotherapy for youths (5 – 17 years of age) diagnosed with bipolar disorder who had been previously stabilized on a combination of lithium and divalproex. This study included subjects who had met criteria for remission for 4 consecutive weeks and were then randomized to either lithium or divalproex for up to 76 weeks. Although limited by a small sample size and absence of a placebo control, the results from this study indicated that lithium and divalproex treatment groups did not differ in time-to-relapse and that divalproex was no different from lithium as a maintenance treatment in youths [107].

As a continuation of the prior study, a prospective, 8-week, open-label, out-patient study to assess the rate of restabilization after combined treatment with lithium and divalproex following a relapse on monotherapy with either agent was conducted. Findling *et al.* found that 34 (89.5%) of the 38 patients responded to combined treatment with lithium and divalproex, whereas 4 patients required adjunctive antipsychotic treatment to address residual symptomatology. These researchers found that reinitiation with the combination mood-stabilizer therapy was well tolerated, indicating that youths who relapse during mood stabilizer monotherapy can be restabilized with a lithium and divalproex combination treatment [108].

Regarding discontinuation of medication for youths with bipolar disorder, the aforementioned expert opinion panel advocated for medication tapering or discontinuation only if the patient has achieved remission for a minimum of 12 – 24 consecutive months. Furthermore, the recommendations include that medications be tapered and not abruptly discontinued, with the taper occurring at a time associated with the lowest possible risk of dysfunction/poor outcomes and with a stable environment and adequate monitoring systems in place. Thus, these expert consensus guidelines should be useful when added to the previous discussed factors in choosing psychotropic agents for patients with PBD.

5. Conclusions

PBD is being increasingly diagnosed and recognized as a chronic mood disorder associated with a significant deterioration in quality of life and impairment of functioning of both the patient and the family. Lithium is the only FDA-approved mood stabilizer for use in the population aged 12 – 18 with mania and along with divalproex and carbamazepine, forms the triad of traditional mood stabilizers used for the initiation of treatment for PBD. There has also been a recent upswing in the use of atypical antipsychotics in PBD. A combination of traditional mood stabilizers along with atypical antipsychotics is commonly used in clinical practice and there is some empirical data to support this combination. There is a dire need for more placebo-controlled, double-blind trials with these psychotropic medications in PBD. Treatment aspects of the depressive phase and also of patients with co-morbid disorders need special consideration. Fortunately, these types of studies are being conducted at present and should add significantly to the database in the next few years. Meanwhile, the available empirical data combined with factors such as adverse effect profile, previous and familial response history, subtype of PBD, phase of illness and co-morbid conditions should help

narrow down the choice of agents to use in monotherapy and combination in PBD.

6. Expert opinion

The field of PBD research is rapidly growing and should continue to yield important data guiding clinical treatment in the near future. The search for safer and more efficacious agents for the treatment of PBD will likely continue to be the focus of much research in the next 5 years. Several pharmaceutical company-sponsored, multisite placebo-controlled trials in PBD are being conducted or have recently been completed, with the results probably having been made public by the time of this publication. Long-term efficacy and safety data regarding the present pharmacologic agents will be made available, allowing the clinician to make better informed decisions.

The identification and diagnosis of PBD will likely gradually drift away from the nosology used in the adult literature and towards development-based distinct features of PBD. Furthermore, in the next 5 – 10 years, biologic markers derived from genetic and brain imaging research in bipolar disorder, will begin to be used clinically to help guide diagnosis and even treatment. These markers will eventually also aid in quantification of risk in children with early symptoms of bipolar disorder, as an important next wave will be more research in identifying children at risk for PBD development, before their first manic episode. This identification will lead to treatment interventions that may prove effective in preventing PBD in at-risk individuals or at least ameliorating its course.

Early identification and accurate diagnosis of PBD in pre-school and school-age children may help lower the morbidity and improve the quality of life in adolescents and adults. With the depressive phase being a common presentation in PBD, especially in adolescents, research and management strategies will target this aspect of the disorder. Further research will also address the question of duration of treatment required in the acute and maintenance phases of PBD. Novel enterprises, such as the Child and Adolescent Psychiatry Network will provide an interactive network for developing evidence-based practice in pediatric psychopharmacology in general and PBD specifically. Research initiatives will also look into potential medication combinations especially to deal with co-morbidities associated with PBD and treatment refractory patients. Finally, psychotherapies specific to PBD will continue to be developed and recognized as an important adjunctive treatment with pharmacotherapy. The continued greater public recognition and more accurate clinician diagnosis of PBD, combined with the increased knowledge gained from pharmacotherapy trials, should serve to start decreasing the significant morbidity and mortality of early onset forms of this disorder.

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