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REVIEW ARTICLE

Pharmacotherapy of bipolar disorder in children and adolescents: an update

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Objective: To review the options for acute and maintenance pharmacological treatment of bipolar disorder in children and adolescents, including the treatment of bipolar depression and comorbid attention deficit/hyperactivity disorder (ADHD).
Methods: Narrative review of randomized clinical trials and open-label studies published from 2000 to 2012. The PubMed and PsycINFO websites were queried. Case series were included when a higher level of evidence was not available.
Results: Published data from randomized controlled trials (RCTs) in acute mania/hypomania with significant responses are available for lithium, topiramate, risperidone, olanzapine, and aripiprazole. Open trials of lithium and lamotrigine show that these drugs may be effective in the treatment of depressive episodes. No trials of selective serotonin reuptake inhibitors (SSRIs) have been conducted. In the treatment of comorbid ADHD, there are encouraging findings with mixed amphetamine salts and atomoxetine; conflicting results are observed with methylphenidate.
Conclusions: Published RCTs of traditional mood stabilizers are scarce, but the best available evidence (results from meta-analytic regression) suggests that second-generation antipsychotics (SGAs) as a group are more effective in reducing manic symptoms. Risperidone was the only one included in head-to-head comparisons (vs. lithium and divalproex), showing superiority in terms of efficacy, but with more metabolic side effects, which were also more common in most of the SGAs. There are few studies addressing the treatment of ADHD and depression. Brazilian guidelines for the treatment of pediatric bipolar disorder should also include some SGAs (especially risperidone and aripiprazole) as first-line treatment, and these drugs should be provided by the public health services.

Keywords: Pediatric bipolar disorder; pharmacotherapy; treatment; lithium; anticonvulsants; atypical antipsychotics

Introduction

Pediatric bipolar disorder (PBD) is a chronic and disabling condition that leads to serious disturbances in the lives of patients and their families.[1] Affected children and adolescents have significantly higher rates of morbidity and mortality compared with healthy children. The impairment in social, family, and academic functioning lead to reduced quality of life.[2,3] In addition, increased rates of suicidal ideation and suicidal behavior are observed.[4] Current data suggest the prevalence of PBD is around 0.1-1%.[5]

In contrast to the robust evidence for pharmacotherapy in adults with bipolar disorder (BD), uncertainties remain regarding the treatment of PBD.[6] As will be seen throughout the text, most recent studies have not addressed the classic antimanic agents, but evidence of the efficacy of atypical antipsychotics is mounting. However, these drugs have also been associated with significant adverse effects, especially weight gain, loss of glycemic control, dyslipidemia, and hyperprolactinemia, making the choice of drug to be used often difficult.[7]

Another aspect that should be taken into account is the high rate of comorbidity with other psychiatric disorders, especially with attention deficit/hyperactivity disorder (ADHD), which is present in more than 40% of patients with PBD in clinical samples and in about 10-15% of children and adolescents in community samples.[8,9] In a 2003 study conducted at Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care center in Southern Brazil, the rate of comorbid ADHD in patients with PBD was 58.3%.[8] Earlier studies have found ADHD rates of 93% in children with BD, 88% in adolescents who had childhood-onset mania, and 59% in adolescents who had adolescent-onset BD.[10] Comorbidity with ADHD is associated with worse functional outcomes and even worse responses to treatment.[11,12]

In view of these issues, the present study sought to review the state of the evidence for pharmacological

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treatment of BD in children and adolescents, including the treatment of comorbid PBD/ADHD.

Methods

This narrative review was conducted by searching the PubMed and PsycINFO websites for the following keywords, individually and two by two: bipolar disorder, adolescent, child, pediatric, juvenile, early-onset, mania, treatment, pharmacotherapy, lithium, valproate, divalproex, carbamazepine, oxcarbazepine, topiramate, lamotrigine, gabapentin, atypical antipsychotics, risperidone, paliperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, combined therapy, and augmentation. Two reviewers (TLP and CPZ) conducted the search independently. When any discrepancies were detected, results were combined. We also assessed the references of other literature reviews. The study included review articles, meta-analyses, randomized clinical trials, and open trials published between 2000 and 2012 in Portuguese, Spanish, and English. Unpublished studies available from other sources, such as the FDA website or symposia annals, were also included. Unpublished data did not undergo peer-review and this should be considered a possible limitation for these studies. Case series and case reports were not included when higher-level evidence was available. References for case series and case reports are available from the authors on request.

Results

The studies found in the review were divided as follows: 1) treatment of mania/hypomania; 2) treatment of bipolar depression; 3) maintenance treatment; and 4) treatment of comorbid ADHD. Within these divisions, they were categorized according to the strength of scientific evidence in the area: a) randomized controlled trials (RCTs) and meta-analyses; b) open, retrospective, or follow-up studies.

Treatment of mania/hypomania/mixed states

Randomized controlled trials/meta-analyses

At the time of this review, our search strategy yielded 15 RCTs[13-27] and two meta-analyses.[28,29]

Geller et al. conducted the first RCT in PBD.[13] Adolescents with BD I or II or major depressive disorder and supposed predictors of bipolarity (delusions, switching to mania during tricyclic antidepressant treatment, marked psychomotor retardation, and BD in a first-degree relative) with comorbid substance use disorder were assessed in a 6-week randomized, double-blind, placebo-controlled trial (DBPCT) using lithium (0.9-1.3 mEq/L) (n=25; age, 16.3±1.2 years). The authors found that lithium was more effective than placebo in improving functioning scores according to the Children Global Assessment Scale (CGAS). Also, the analysis of urine drug assays was significantly different for the lithium (n=13) vs. the placebo (n=12) groups, but there was no between-group difference in measures of mood symptoms according to the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) mood items. There were limitations in the study due to the fact that the diagnosis of BD was made in a flexible way, allowing entry of patients with clinical depression and predictors of future bipolarity into the protocol. Polyuria was the most frequent adverse effect.

Kowatch et al. conducted an 8-week RCT of divalproex, lithium, or placebo (unpublished, presented at an AACAP meeting) in 153 subjects aged 7 to 17 years with BD I in manic or mixed episode.[14] Response was defined as Clinical Global Impressions-Improvement scores of 1 or 2 (very much or much improved). Response rates were: 54% for divalproex; 42% for lithium; and 29% for placebo. Lithium showed a trend toward efficacy but did not clearly separate from placebo. Effect sizes for lithium and divalproex were moderate.

Wagner et al. evaluated the efficacy of divalproex extended-release (ER) as monotherapy for PBD during a DBPCT in 150 patients (manic or mixed episode, aged 10-17 years).[15] Divalproex was given to a maximum dosage of 35 mg/kg/day (serum levels: 80 to 125 μg/mL) during 4 weeks. Concomitant use of antipsychotics, antidepressants, or other mood stabilizers was not allowed. Participants were assessed with the Young Mania Rating Scale (YMRS), the Clinical Global Impression – Severity scale (CGI-S), the Clinical Global Impression – Improvement scale (CGI-I), and the Children's Depression Rating Scale – Revised (CDRS-R). There was no significant difference between the placebo and divalproex ER groups in YMRS total score (-8.8 vs. -7.9 respectively, $p = 0.604$) or in secondary measures. Divalproex was similar to placebo in the incidence of adverse effects, except for weight gain, which was higher in the divalproex ER group. The most common adverse events were headache and vomiting.

A 6-week double-blind, randomized trial of risperidone (0.25-2 mg/day) plus placebo vs. divalproex (60-120 μg/mL) plus placebo was conducted by Pavuluri et al. in 66 patients aged 8-18 years.[16] Reduction in YMRS scores was the primary efficacy measure. The secondary measures were the CDRS-R, the CGI-BP, the Overt Aggression Scale (OAS), and the Brief Psychiatric Rating Scale for Children (BPRS-C). Response rates were defined as $\geqslant$ 50% improvement in YMRS for mania and $\geqslant$ 50% improvement in CDRS-R for depression. The rates achieved for manic symptoms were 78.1% for risperidone vs. 45.5% for divalproex ($p < 0.01$); and for depressive symptoms, 65.6% for risperidone vs. 42.4% for divalproex ($p < 0.1$). The remission rates (YMRS $\leqslant$ 12 and CDRS-D $\leqslant$ 28) were 62.5% with risperidone vs. 33.3% with divalproex ($p < 0.05$). There were no significant differences in weight gain. The dropout rate was 24% in the risperidone group vs. 48% in the divalproex group, mostly due to increased irritability.

Another divalproex DBPCT was conducted in 30 adolescents (age 12-18 years) with bipolar I manic or mixed episode by DelBello et al.[17] Patients received an initial dose of divalproex, 20 mg/kg, and were then

randomized to receive adjunctive quetiapine (maximum dose of 450 mg/day) or placebo, for 6 weeks. The primary efficacy measure was change in YMRS scores. The quetiapine group demonstrated a greater reduction in YMRS scores compared with the placebo group ($p = 0.03$). In addition, the YMRS response rate was significantly higher the in divalproex + quetiapine group than in the placebo + divalproex group (87 vs. 53%, $p = 0.05$). Sedation was the main adverse effect, and was significantly more common in the quetiapine group.

A DBPCT investigated the use of oxcarbazepine monotherapy in 116 youths with BD in manic or mixed episode.[18] The patients were allocated to receive flexible doses of oxcarbazepine (maximum dose 900-2,400 mg/day) or placebo for 7 weeks. The primary efficacy measure was the mean change from baseline to endpoint in the YMRS. Oxcarbazepine monotherapy (mean dose 1,515 mg/day) did not significantly improve YMRS scores at endpoint compared to placebo. The oxcarbazepine group reported the occurrence of dizziness, nausea, somnolence, diplopia, fatigue, and rash with an incidence at least twice that of the placebo group.

A pilot DBPCT with 56 children and adolescents (age 6-17 years) with a diagnosis of bipolar I disorder receiving topiramate (n=29) or placebo (n=27) was conducted to analyze the efficacy of topiramate monotherapy for acute mania in children and adolescents.[19] Efficacy measures included the YMRS, BPRS-C, CDRS, the CGAS, and the CGI-I. However, the study was discontinued prematurely when trials on the use of topiramate in adults with mania showed no efficacy. In the short period in which the study was conducted, the only statistically significant differences observed were in variation in the YMRS ($p = 0.003$) and BPRS-C ($p = 0.048$). Adverse events of topiramate included decreased appetite, nausea, diarrhea, and paresthesia.

A DBPCT including 169 children and adolescents (age 10-17 years) diagnosed with bipolar I disorder, experiencing a manic or mixed episode, in which participants were randomized to receive placebo (n=50), risperidone 0.5-2.5 mg/day (n=61), or risperidone 3-6 mg/day (n=58) for 3 weeks was conducted by Haas et al.[20] Subjects were assessed using the YMRS, the CGI-I, the Clinical Global Impression–Bipolar (CGI-BP) scale, and the BPRS-C. Significant improvement in the YMRS score was observed in both risperidone groups as compared with placebo ($p < 0.001$). Twenty-six percent of subjects receiving placebo achieved a clinical response, compared with 59% in the 0.5-2.5 mg risperidone group ($p = 0.002$) and 63% in the 3-6 mg risperidone group ($p < 0.001$). The adverse events most commonly associated with risperidone were somnolence, headache, and fatigue (dose-dependent increase in percentage), as well as moderate weight gain. The study results suggest that the lower dose range is associated with a better safety profile.

An 8-week RCT was conducted by Geller et al. with 279 children and adolescents aged 6 to 15 years.[21] Subjects were randomly assigned to receive risperidone (4-6 mg), lithium (1.1-1.3 mEq/L), or divalproex sodium (111-125 μg/mL). The primary outcome measure was the Children Global Impressions for Bipolar Illness Improvement–Mania (CGI-BP-IM). Patients were also assessed with the Modified Side Effects Form for Children and Adolescents and the K-SADS – Mania Rating Scale (KMRS). Patients in the risperidone group had a significantly higher response rate than those treated with lithium (68.5 vs. 35.6%; $p < 0.001$) or those treated with divalproex sodium (68.5 vs. 24.0%; $p < 0.001$). There was no significant difference in response rates between the lithium and the divalproex groups. Mean weight gain was significantly greater with risperidone than lithium (3.31 vs. 1.42 kg; $p < 0.001$) and divalproex sodium (3.31 vs. 1.67 kg; $p < 0.001$). Greater increases in body mass index and prolactin levels were detected in subjects treated with risperidone.

A 3-week multicenter DBPCT was conducted by Tohen et al. with 161 adolescents aged 13-17 years with an acute manic or mixed episode.[22,30] Subjects received either olanzapine at flexible doses (2.5-20 mg/day [n=107]) or placebo (n=54). There was a significantly greater reduction in the YMRS scores of patients receiving olanzapine than in the placebo group (-17.65 vs. -9.99; $p \leqslant 0.001$). The mean weight change was significantly greater for patients receiving olanzapine relative to patients receiving placebo (3.7 vs. 0.3 kg; $p \leqslant 0.001$), as was the frequency of other side effects, such as drowsiness and sedation. Furthermore, in the olanzapine group, significant increases in systolic blood pressure ($p = 0.001$), fasting glucose ($p < 0.002$), total cholesterol ($p < 0.001$), serum prolactin levels ($p < 0.001$), and liver enzymes (AST, $p < 0.002$; ALT, $p < 0.003$) were reported.

The effectiveness of quetiapine in the treatment of acute manic episodes associated with BD in children and adolescents aged 10 to 17 years was demonstrated in a 3-week DBPCT.[23,31] Patients were randomized to receive quetiapine 400 mg/day (n=95), quetiapine 600 mg/day (n=98), or placebo (n=91). Quetiapine 400 mg/day and 600 mg/day were statistically superior to placebo, according to changes in YMRS scores ($p < 0.001$ for both doses vs. placebo). Improved functioning according to the CGAS scores was also observed.

A 4-week DBPCT was designed by DelBello et al. to evaluate the efficacy of ziprasidone compared to placebo in 238 children and adolescents aged 10-17 years with BD-I.[24,28] The target dose was 80-160 mg/day for subjects weighing > 45 kg and 40-80 mg/day for children weighing < 45 kg. The primary efficacy measure was the change in YMRS total score. A reduction $> 50\%$ in YMRS was achieved in 62% of the subjects in the ziprasidone group, compared to 35% of the subjects in the placebo group ($p < 0.001$). Difference from placebo was only achieved at week 4. Patients receiving ziprasidone 40-80 mg/day showed less improvement than the group receiving 80-160 mg/day, but it was unclear whether this difference was due to the dose or to a weight effect, since the dosing mechanism is related to patient weight. The most frequent side effects among patients treated with ziprasidone were dystonia, headache, and sedation.

Aripiprazole demonstrated statistically significant superiority over placebo in the treatment of acute mania or mixed states in a 4-week DBPCT (n=296).[22,25] Patients were randomized to receive aripiprazole 10 mg, aripiprazole 30 mg, or placebo during a 4-week acute phase and then continued the allocated treatment for over 26 weeks. A reduction of at least 50% in YMRS total score at week 4 was achieved by 44.8%, 63.6%, and 26.1% of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups respectively ($p < 0.01$ for both doses vs. placebo). Adverse events were mild to moderate for the two aripiprazole subgroups, with somnolence, parkinsonism, and akathisia being most frequent.

A DBPCT conducted at the HCPA Department of Child and Adolescent Psychiatry (n=43, 8-17 years) included patients with BD in manic/mixed episode comorbid with ADHD.[26] Patients were randomized to receive placebo or aripiprazole monotherapy to the maximum dose of 20 mg/day for 6 weeks. The aripiprazole group had a greater reduction in outcome parameters (YMRS, Children Mania Rating Scale – Parent version [CMRS-P] and CGI-S), higher rates of response and remission, and a significant reduction in ADHD symptoms despite no use of concomitant stimulant medication. The most common adverse events reported by the aripiprazole group were somnolence and drooling.

Regarding alternative treatments, a 16-week DBPCT of flax oil was conducted on 51 subjects with BD aged 6-17 years.[32,27] Patients had a previous failure in symptom stabilization and/or were intolerant to lithium and/or valproate and/or atypical antipsychotic therapy, or desired participation in a study without conventional treatment. The oil contained the omega-3 fatty acid α-linolenic acid (α-LNA). Patients were randomly assigned to receive supplementation with flax oil, containing 550 mg α-LNA/g (maximum dosage: 12 capsules/day) or an olive oil placebo adjunctively or as monotherapy. No difference between flax oil or placebo was detected in the measures of mood symptoms and global functioning (YMRS, CDRS-R, and CGI-BP).

No DBPCTs of carbamazepine, lamotrigine, gabapentin, paliperidone, or clozapine were identified by our literature review. A summary is presented in Table 1.

Biederman et al. conducted a meta-analysis comparing open-label studies and randomized placebo-controlled trials (RPCTs) to evaluate the accuracy of information provided by open-label studies as predictors of the findings of RPCTs.[28] Fourteen studies were included (19 observations: 11 open-label trials and 8 RPCTs) of second-generation antipsychotics (SGAs) and mood stabilizers. Similarities between the effects of treatment reported in open-label studies and RPCTs were found, suggesting that open studies may predict treatment safety and efficacy. Furthermore, a higher YMRS result difference was found for risperidone in RPCTs than in open-label studies. There were no other significant differences between open-label studies and RPCTs with other individual medications evaluation.

Liu et al. conducted a systematic review of the available literature on the effectiveness of agents for the treatment of mania, depression, and ADHD in children and adolescents.[29] The review included 29 open-label studies and 17 RPCTs covering 2,666 individuals and evaluated mood stabilizers, SGAs, and naturopathic compounds (flax oil and omega-3). Modest effects were reported for traditional antimanic agents, such as lithium carbonate, divalproex sodium, and carbamazepine, when used as monotherapy. The SGAs as a group were significantly more effective than mood stabilizers and naturopathic compounds on meta-analytic regression of RCTs. No significant difference was observed between risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole (for which RPCTs are available). However, SGAs were also associated with increased rates of weight gain and somnolence.

A review of the available literature shows that risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have a large effect in reducing YMRS scores. RPCTs of traditional mood stabilizers are scarce, but the best available evidence (results from meta-analytic regression) suggests SGAs are more effective in reducing manic symptoms. Correll et al. conducted a comparative analysis of RPCTs of SGAs and mood stabilizers.[39] Nine RPCTs enrolling young patients were found (five evaluating SGAs and four about mood stabilizers). The results of the study show that SGAs may be more effective in reducing manic symptoms than mood stabilizers. Head-to-head comparisons are also scarce. The two available studies suggest risperidone is more effective than lithium and divalproex, but more metabolic adverse events were associated with risperidone use. In these studies, divalproex seemed to be more effective than lithium.

Open-label studies

Our search strategy yielded 20 open-label, retrospective, or follow-up studies available in the literature at the time the review was concluded. Data are summarized in Table 2.[40-59] Case reports and case series were detected, but were not included in the text due to the availability of higher-level evidence for the psychopharmacological agents of interest. Nevertheless, we recommend analysis of these case series and reports, which are available from the authors on request.

Kowatch et al. conducted an open-label study of lithium, divalproex sodium, or carbamazepine (n=42) for 6 weeks.[58] All three drugs were found effective. There were no significant differences between the three drugs.

In an open trial of carbamazepine (788±252 mg daily, n=27, 8 weeks), 16 (59%) children completed the study, and treatment with carbamazepine was associated with statistically significant, though modest, levels of improvement in mean YMRS scores (10.1±10.2, $p < 0.001$), suggesting lack of complete resolution of mania.[59]

Biederman et al. conducted a 12-week, open-label, prospective trial with 39 subjects (age 6-17 years) using lamotrigine monotherapy at doses ranging from 160.7±128.3 mg/day in subjects < 12 years (n=22) to

Table 1 Randomized controlled trials assessing pharmacotherapy for children and adolescents with bipolar disorder

Authors/year	Medication	Dosage range	Subjects	Duration	Result	Limitations/observations/adverse effects*
Geller, 1998[13]	Li vs. Pc	0.9-1.3 mEq/L	25	6 weeks	Li = Pc in YMRS Li > Pc in CGAS	Polyuria
Kowatch, 2007[14]	Li vs. DVP vs. Pc	N/A	153	8 weeks	DVP > Pc Li = Pc	N/A
Wagner, 2009[15]	DVP vs. Pc	35 mg/kg/day	150	4 weeks	DVP = Pc	Weight gain
Pavuluri, 2010[16]	Risp + Pc vs. DVP + Pc	Risp 0.25-2 mg/day DVP 60-120 μg/mL	66	6 weeks	Risp > DVP	No difference in weight gain
DelBello, 2002[17]	DVP + Quet vs. DVP + Pc	DVP 20 mg/kg/day Quet 450 mg/day	30	6 weeks	DVP + Quet > DVP + Pc	Sedation
Wagner, 2006[18]	OXC	900-2,400 mg/day	116	7 weeks	OXC = Pc	Dizziness, nausea, diplopia, somnolence, fatigue, and rash
DelBello, 2005[19]	TPT	200-400 mg/day	56	4 weeks	TPT > Pc	Decreased appetite, nausea, diarrhea, and paresthesias
Haas, 2009[20]	Risp	0.5-2.5 mg/day or 3-6 mg/day	169	3 weeks	Risp > Pc	Weight gain, somnolence, headache, and fatigue
Geller, 2012[21]	Risp vs. Li vs. DVP	4-6 mg/day 1.1-1.3 mEq/L 111-125 μg/mL	279	8 weeks	Risp > Li Risp > DVP Li = DVP	Increases in BMI and hyperprolactinemia
Tohen, 2007[22]	Olan	2.5-20 mg/ml	161	3 weeks	Olan > Pc	Weight gain, drowsiness, sedation, increases in systolic blood pressure, fasting glucose, total cholesterol, serum prolactin levels, and liver enzymes
FDA, 2009[23]	Quet	400 mg/day or 600 mg/day	284	3 weeks	Quet > Pc	Sedation, dizziness, headache, and fatigue
FDA, 2009[24]	ZPS	60-80 mg/day or 120-160 mg/day	238	4 weeks	ZPS > Pc	Dystonia, headache, and sedation
Findling, 2009[25]	Arip	10 mg or 30 mg/day	296	4 weeks	Arip > Pc	Somnolence, parkinsonism, and akathisia
Tramontina, 2009[26]	Arip	20 mg/day	43	6 weeks	Arip > Pc	Somnolence and drooling
Gracious, 2010[27]	Flax oil	12 capsules/day (550 mg α-LNA/g)	51	16 weeks	Flax oil = Pc	14% discontinued due to mood-related issues, 30% due to other clinical issues, and 53% for any other reason
Depressive episode						
DelBello, 2009[33]	Quet	300-600 mg/day	32	8 weeks	Quet > Pc	Dizziness
Maintenance treatment						
Kafantaris, 2003[34]	Li	0.6-1.2 mEq/L	40	2 weeks	Li > Pc	
Findling, 2005[35]	Li vs. DVP	Li: 0.6-1.2 mmol/L DVP: 50-120 μg/mL	139	76 weeks	Li = DVP	Increased thirst, emesis, and enuresis with lithium; headache and stomach pain with DVP
Findling, 2012[36]	Arip	6.4±2.1 mg/day	60	72 weeks	Arip > Pc	Stomach pain, increased appetite, headaches
Comorbidity with ADHD						
Scheffer, 2005[37]	DVP + MAS	DVP: 82.4 μg/mL MAS: 14.5 mg/mL	30	4 weeks	DVP + MAS > DVP + Pc	Abdominal pain, diarrhea, nausea, appetite increase, headache, drowsiness, difficulty falling asleep, irritability, and rash
Findling, 2007[38]	MPH	5-10 mg	16	4 weeks	MPH = Pc	One subject discontinued due to urticaria and vomiting; a second subject discontinued due to increases in serum alkaline phosphatase and liver transaminases
Zeni, 2009[11]	Arip + MPH vs. Arip + Pc	MPH: 0.3-0.7 mg/kg/day Arip: 10-20 mg	16	2 weeks with each treatment option	Arip + MPH = Arip + Pc	One patient discontinued the trial due to severe mixed episodes

Arip = aripiprazole; CGAS = Children Global Assessment Scale; DVP = divalproex sodium; Li = lithium; MAS = mixed amphetamine salts; MPH = methylphenidate; N/A = data not available; Olan = olanzapine; OXC = oxcarbazepine; Pc = placebo; Quet = quetiapine; Risp = risperidone; TPT = topiramate; YMRS = Young Mania Rating Scale; Zps = ziprasidone.
* Adverse effects significantly more frequent in the active medication group vs. placebo.

Table 2 Open-label, retrospective, or follow-up studies of the treatment of mania, hypomania or mixed episodes, depressive episodes, maintenance therapy, and comorbidity with attention deficit/hyperactivity disorder

Study design	Authors/year	Medication	Dosage range	Subjects	Duration	Result	Limitations/observations/adverse effects*
Treatment of manic, hypomanic, or mixed episodes							
Open-label	Kafantaris, 2003[40]	Li	0.6-1.2 mEq/L	100	4 weeks	63 of 100 subjects responded; 26 of 100 achieved remission	Adjunctive antipsychotics were used in 46% of subjects
Follow-up	Pavuluri, 2005[41]	DVP	50-120 μg/mL	34	6 months	73.5% response rate* 52.9% remission rate	Dropout rate: 6.4%, due to benign rash
Open-label	Wagner, 2002[42]	DVP	45-125 μg/mL	40	2-8 weeks	61% response rate*	10% used adjunctive therapy with Li and 53% used other drugs simultaneously
Open-label	Kowatch, 2000[58]	Li, DVP, and CBZ	Li: 0.8-1.2 mEq/L DVP: 85-110 μg/L CBZ: 7-10 μg/L	42	6 weeks	Response rates were as follows: DVP, 53%; Li, 38%; CBZ, 38%*	All three mood stabilizers were well tolerated, with no serious adverse effects
Open-label	Joshi, 2010[59]	CBZ	788±252 mg/day	16	8 weeks	Modest levels of improvement in YMRS scores	Suggests lack of complete resolution of mania
Open-label	Pavuluri, 2009[43]	Lamotrigine	150-200 mg/day	46	14 weeks	Response rate: 72% for manic symptoms and 82% for depressive symptoms†	Benign rash in 6.4% of subjects
Open-label	Biederman, 2010[44]	Lamotrigine	160.7±128.3 mg/day (subjects < 12 years); 219.1±172.2 mg/day (subjects > 12 years)	39	12 weeks	Response rates: 66% (< 12 years) and 54% (> 12 years)†	25% of subjects discontinued the trial due to adverse events, mostly dermatological
Open-label	Pavuluri, 2006[51]	Li + Risp	Li: 0.6-1.0 mEq/L Risp: 2 mg/day	38	11 months	Response rate: 85.7%*	Weight gain, nausea/vomiting, increased appetite, stomach pain, sedation, polyuria, enuresis, tremor, restlessness, muscle stiffness, fatigue, cognitive dulling, flu-like symptoms
Open-label	Pavuluri, 2004[52]	Risp + Li vs. Risp + DVP	Risp: 3 mg/day; Li: 0.6-1.0 mEq/L; DVP: 50-120 μg/mL	37	6 months	Response rates (⩾ 50% change from baseline YMRS score at the end of study): 80% for DVP + Risp and 82.4% for Li + Risp	Combination therapy was well tolerated in both groups. Two subjects discontinued earlier in Risp + Li group due to enuresis and fatigue
Open-label	Wozniak, 2009[54]	Olan vs. Olan + topiramate	Monotherapy: Olan 8.6±3.4 mg/day Combined: Olan 9.9±5.2 and topiramate 70.5-30.5 mg/day	40	8 weeks	Statistically significant reduction in YMRS scores with both treatments	"Spacey", tremor, akathisia, "dazed", nystagmus, speech deterioration
Open-label	Biederman, 2005[53]	Olan vs. Risp	Olan: 10 mg/day Risp: 2 mg/day	31	8 weeks	Response rates: 69% for Risp and 53% for Olan†	Preschoolers. Weight gain observed with both drugs Higher prolactin levels with Risp
Open-label	Biederman, 2005[45]	Risp	1.25±1.5 mg/day	30	8 weeks	Significant decrease in YMRS (average 14.4 points)	Eight dropouts (seven due to lack of efficacy and one due to orthostatic hypotension)
Open-label	Frazier, 2001[46]	Olan	2.5-20 mg/day	23	8 weeks	61% of response rate†	Increase of body weight
Retrospective	Marchand, 2005[47]	Quetiapine	397.4±221.4 mg/day	32	6.1±5.9 months	50% of subjects symptom improvement	14 were on quetiapine monotherapy
Open-label	Biederman, 2007[48]	Ziprasidone	57.3±33.9 mg/day	21	8 weeks	Improvement in mean YMRS and CGI-I scores	Sedation, headache, and gastrointestinal problems

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Table 2 Continued

Study design	Authors/year	Medication	Dosage range	Subjects	Duration	Result	Limitations/observations/adverse effects*
Open-label	Tramontina, 2007[49]	Aripiprazole	2-20 mg/day	10	6 weeks	Improvement in global functioning scores ($p = 0.01$), manic symptoms ($p < 0.01$), and ADHD symptoms ($p < 0.01$)	Sialorrhea, tiredness, sedation, confusion, depressive symptoms, increased appetite or decreased appetite, sweating, tremors, nervousness, and anxiety
Open-label	Findling, 2011[50]	Aripiprazole	15 mg/day	69	16 weeks	62.5% met response criteria[§]	Stomachache, headache, and increased appetite
Open-label	Wozniak, 2006[56]	Omega-3 fatty acid	1,290-4,300 mg/day	20	8 weeks	35% of subjects had improvement in symptoms ($\geq$ 50% decrease in YMRS)	Small but statistically significant weight gain
Open-label	Rucklidge, 2010[57]	Micronutrient formula (EMPowerplus)	15 capsules of micronutrient formula[‖]	120	3-6 months	43% decline in PBD symptoms and 40% in ADHD symptoms, evaluated by LOCF	Data obtained from the formula manufacturer's database
Depressive episode							
Open-label	Patel, 2006[60]	Li	1.0-1.2 mEq/L	27	6 weeks	48% response rate[¶]	Headache, nausea/vomiting, stomachache, abdominal cramps
Open-label	Chang, 2006[61]	Lamotrigine	100-200 mg/day	20	8 weeks	63% response rate[¶]	No significant adverse effects
Review of medical records	Biederman, 2000[62]	SSRIs and mood stabilizers	**	59	**	Significant improvement of bipolar depression with SSRI. Improvement of manic symptoms with mood stabilizers	Recurrence of manic symptoms with SSRI. Mood stabilizers did not change course of bipolar depression
Maintenance treatment							
Open-label	Findling, 2005[63]	Li or DVP (monotherapy vs. combination)	Li: 0.6-1.0 mmol/L DVP: 50-100 μg/L	38	8 weeks	Patients who became symptomatic with monotherapy had a 89.5% remission rate with combination therapy	Five patients discontinued study participation due to adverse events (alopecia in both groups; increased thyrotropin blood level and thrombocytopenia in DVP group; enuresis in Li group)
Open-label	Tramontina, 2007[64]	Topiramate	50-150 mg/day	10	11 weeks	Significant reduction in YMRS scores and in body weight	Cognitive impairment
Open-label	Duffy, 2009[65]	Quetiapine	50-800 mg/day	18	48 weeks	Effective and well tolerated	Somnolence and flu-like symptoms
Comorbidity with ADHD							
Open-label	Chang, 2009[66]	Atomoxetine	1.2 mg/kg	12	8 weeks	67% response rate; 50% remission rate	Two subjects discontinued due to worsening of mood symptoms

ADHD = attention deficit/hyperactivity disorder; CBZ = carbamazepine; CGI-I = Clinical Global Impression – Improvement scale; DVP = divalproex sodium; Li = lithium; LOCF = last observation carried forward; Olan = olanzapine; Risp = risperidone; SSRI = selective serotonin reuptake inhibitors; YMRS = Young Mania Rating Scale.
* Defined as a reduction in YMRS scores $\geq$ 50%.
† Defined as a score less than 12 on the YMRS. Response for depressive symptoms was defined as a score less than 40 on the Children's Depression Rating Scale – Revised (CDRS-R).
‡ Defined as a reduction in YMRS scores $\geq$ 30%.
§ Response criteria consisted of 3 of 4 consecutive weeks with: 1) CDRS-R $<$ 29; 2) YMRS $<$ 10; and 3) Children Global Assessment Scale (CGAS) $>$ 50.
‖ The ingredients of the formula are listed on the developer's website (Truehope.com).
¶ Defined as reduction in CDRS-R scores $\geq$ 50%.
** Data not included in table due to the nature of the study.

219.1±172.2 mg/day in children 12-17 years old (n=17).[44] Patients were assessed with the YMRS, the CGI-I, CDRS, and BPRS. The response rates, defined as a reduction in YMRS scores ⩾ 30% or improvement of mania on CGI-I (⩽ 2), was 66%; 54% of the subjects had a reduction in YMRS scores ⩾ 50% ($p < 0.001$). Lamotrigine was also associated with improvement in depressive, ADHD, and psychotic symptoms, but 25% of the patients discontinued the trial due to adverse events, dermatologic side effects being the most common.

In open trials of combination treatment, risperidone as an augmentation agent in patients exhibiting poor response to lithium (n=38) was effective and well tolerated, with response rates of 85.7% (defined as a decrease in the YMRS ⩾ 50%).[51] Divalproex sodium plus risperidone or lithium plus risperidone in 37 patients promoted significant improvement in the YMRS, the CDRS-R, and the CGI-BP ($p < 0.001$). There were no significant between-group differences in terms of efficacy, safety, or tolerability.[52]

Wozniak et al. conducted an open trial evaluating 40 patients aged 6 to 17 years, comparing olanzapine monotherapy with the combination of olanzapine plus topiramate.[54] The topiramate group presented a reduced weight gain, but the combination was not superior to olanzapine monotherapy in reducing manic symptoms.

Biederman et al. evaluated the use of olanzapine (6.3±2.3 mg/day) or risperidone (1.4±0.5 mg/day) monotherapy in 31 preschoolers (age 4-6 years) in an 8-week open trial.[53] The primary efficacy measures were a reduction ⩾ 30% in the YMRS and improvement in the CGI scale. Both antipsychotics proved to be effective in reducing manic symptoms. There was no difference in response rate between risperidone and olanzapine (69% vs. 53%, $p = 0.4$). Weight gain was observed with the two drugs. Significantly higher prolactin serum levels were observed with risperidone.

Masi et al. assessed the effect of clozapine in 10 subjects (age 12 to 17 years).[55] Improvements measured with CGI-I, YMRS, BPRS, CGA, and CGAS were significant ($p < 0.001$). The average clozapine dose was 75-300 mg/day. The most common side effects were increased appetite, sedation, enuresis, and sialorrhea. There was a 10.7% mean increase in body weight.

Rucklidge et al. researched the effect of the intake of a micronutrient formula, composed essentially of vitamins and minerals (EMPower), for 3-6 months in 120 subjects aged 7-18 years with BD.[57] Around 80% of these patients were on psychiatric medication and 24% reported comorbidity with ADHD. The data were obtained from the formula manufacturer's database. Clients were asked to complete a daily symptom checklist based on the DSM-IV and send it to the company over the internet, fax, or phone. About 46% of patients experienced > 50% improvement in BD symptoms, but 38% of the sample continued to require psychotropic medication.

Open-label studies evaluating treatment options for mania exhibit similar results to those found in RCTs. The SGAs are effective in reducing effect measures, as do most mood stabilizers, with the exceptions of topiramate and carbamazepine. Open-label studies of alternative treatments exhibited modest results.

Treatment of bipolar depression

Randomized controlled trials/meta-analyses

At the time of this review, only one RCT about treatment of bipolar depression had been published. DelBello and colleagues conducted a DBPCT of quetiapine in 32 subjects (age 12-18 years) with BD in a current depressive episode.[33] Subjects underwent a 300-600 mg trial of quetiapine or placebo for 8 weeks. Treatment response was defined as a reduction in CDRS-R ⩾ 50%. There was no statistically significant difference between the placebo and quetiapine groups in changes in CDRS-R scores from baseline to endpoint ($p = 0.89$), response rates (placebo = 67% vs. quetiapine = 71%), or change in secondary efficacy measures. The most frequent side effect of quetiapine was dizziness.

Open-label studies

Our search strategy yielded three open-label studies.[60-62] A 6-week open-label study of 27 adolescents aged 12 to 18 years with bipolar I disorder experiencing an acute depressive episode was conducted by Patel et al. to examine the effectiveness of lithium in decreasing depressive symptoms.[60] The subjects received lithium 30 mg/kg, which was adjusted to achieve a therapeutic serum level of 1.0-1.2 mEq/L. Response rates, defined as a reduction in CDRS-R score ⩾ 50%, occurred in 48% of the subjects. Thirty percent of the patients achieved remission (CDRS-R score ⩽ 28 and a CGI-BP Improvement score of 1 or 2) with lithium monotherapy. The most common side effects were headache (74%), nausea/vomiting (67%), stomachache (30%), and abdominal cramps (19%).

An 8-week open-label trial of lamotrigine was conducted by Chang et al. with 20 adolescents (ages 12-17 years) with BD experiencing a depressive episode, using lamotrigine as monotherapy or with other mood stabilizer and/or stimulant drug (if ADHD was diagnosed).[61] The primary measures of response were improvement on the CGI at week 8 and a decrease of at least 50% in the CDRS-R scores; these endpoints were achieved in 84% and 63% of the subjects, respectively. Significant decreases in the YMRS ($p = 0.001$) and the Overt Aggression Scale-Modified scores ($p = 0.001$) were observed. No significant adverse effects were reported during the trial.

A retrospective review of medical records of 59 patients with PBD was conducted by Biederman et al., evaluating the use of selective serotonin reuptake inhibitors (SSRIs) and mood stabilizers in bipolar depression.[62] SSRIs were associated with significant improvement of bipolar depression, but increased the chances of recurrence of manic symptoms. Furthermore, the use of mood stabilizers was found to improve manic symptoms, but did not change the course of bipolar depression. SSRIs did not modify the improvement of manic symptoms obtained

with mood stabilizers. In conclusion, this review suggests that treatment of bipolar depression in children and adolescents can be performed with an SSRI, as long as it is preceded by adequate control of manic symptoms with mood stabilizers. Prospective studies are urgently needed to confirm this finding.

There are few studies regarding bipolar depression in children and adolescents, and all the available trials have limitations, such as small sample sizes and lack of a placebo group. Based on current studies, lithium (monotherapy) and lamotrigine (monotherapy or adjunctively) seem to be effective treatments. SSRIs may be an alternative to treat depressive symptoms, but current studies suggest their use only when combined with antimanic agents. Studies on this topic are urgently needed.

Maintenance treatment

Randomized controlled trials

Our search strategy yielded three RCTs on maintenance treatment.

As a continuation of the open-label study of lithium carried out by Kafantaris et al., a DBPCT phase was conducted.[34] Adolescents who initially responded to lithium were randomly assigned to lithium or placebo for 2 weeks. The results suggested that both lithium and the placebo had similar rates of symptoms exacerbation (52.6% for lithium; 61.9% for placebo). Despite promising results in the open-label study phase, a large treatment effect for lithium was not found in the maintenance phase.

Of 139 subjects aged 5-17 years who were initially treated with lithium combined with divalproex, 60 patients were randomly assigned to discontinue one of the agents for 76 weeks, while the others were kept on combination therapy.[35] There was no difference in time to recurrence of symptoms between the lithium and divalproex monotherapy groups. Receiving both drugs again promoted remission rates of 89.5%.

As a continuation of an open-label study of aripiprazole monotherapy with 96 subjects (age 4-9 years), Findling et al. conducted a DBPCT with 60 patients from the initial study who achieved remission and stabilization.[36] These patients were randomly assigned to receive aripiprazole (mean dose: 6.4±2.1 mg/day) or placebo for 72 weeks. The primary outcome measure for this phase of the trial was time to discontinuation due to a mood event. The median (± standard error) time in weeks to discontinuation was longer in the aripiprazole group (6.14±11.88; $p = 0.005$) than with placebo (2.29±0.38; $p = 0.003$), leading to the conclusion that aripiprazole may be a more effective long-term treatment than placebo. The most common side effects with aripiprazole were stomach pain, increased appetite, and headaches.

Open-label studies

Three open-label studies were detected.

An 8-week prospective, open-label trial was conducted by Findling et al. in 38 patients aged 5 to 17 years with BD I or II who remitted with combination therapy consisting of lithium and divalproex.[63] The main issue raised by the authors was whether patients who achieved stability on combination drug therapy would benefit from receiving more than one drug during long-term treatment. For this purpose, patients subsequently discontinued one of the agents. Those who became symptomatic during maintenance monotherapy with lithium or divalproex presented an 89.5% remission rate when treated with the same combination, according to the YMRS, CDRS-R, CGAS, and CGI-S.

An 11-week open trial was conducted by Tramontina et al. with 10 patients (age 11-17 years) who were previously on a single mood stabilizer or antipsychotic and presented weight gain greater than 5%.[64] The subjects were enrolled to switch to topiramate. The main hypothesis was that topiramate monotherapy would be able to maintain mood stabilization while reducing body weight. There was a significant reduction in YMRS scores ($p < 0.01$) as well as in body weight ($p < 0.01$).

A 48-week open-label prospective study was conducted by Duffy et al. with 18 patients aged 13 to 20 years and meeting DSM-IV lifetime criteria for BD type I, II, or NOS.[65] Initially, for 8 weeks, patients received quetiapine in increments of 50 mg daily to a maximum of 800 mg/day according to improvement of clinical symptoms. Simultaneously, other psychotropic drugs previously in use were discontinued if possible. Concomitant use of clonazepam or zopiclone for insomnia was allowed. Five patients required combination therapy. In that trial, quetiapine was effective and well tolerated. CGI-S scores declined over the course of the trial ($p < 0.01$). The most common side effects were somnolence and flu-like symptoms.

Maintenance treatment is mandatory due to the high recurrence rates in PBD. The effect of combined lithium and divalproex sodium therapy is controversial: in an open-label trial, it seemed effective, but this result was not replicated in a later RCT. Topiramate showed effectiveness in reducing YMRS scores and weight after mood stabilization with other agents. Quetiapine has also demonstrated a positive response. However, high-level evidence is scarce. Most drugs were not assessed in long-term treatment trials. Studies where even one of the agents was discontinued revealed faster recurrence of symptoms. The current expert recommendation is maintenance of the same medication and dosage with which the patient was initially stabilized and management of comorbidities.

Comorbid PBD/ADHD

Randomized controlled trials

Our search strategy yielded three RCTs of patients with comorbid PBD/ADHD.

Scheffer et al. conducted a two-stage trial wherein patients who had achieved mood stabilization with divalproex sodium, but no significant improvement of ADHD symptoms, were invited to join a 4-week

randomized, crossover DBPCT of mixed amphetamine salts (n=30, age 8-17 years).[37] Significant improvement in ADHD symptoms was observed in the MAS group, while no significant between-group change in the YMRS was detected. Mixed amphetamine salts were considered safe and effective without promoting destabilization of BD.

Findling et al. conducted a 4-week crossover DBPCT of methylphenidate in 16 children and adolescents with BD/ADHD previously on mood stabilizers, with residual ADHD symptoms.[38] Best dose week of treatment (5 mg-10 mg-15 mg) was compared to placebo and a significant difference was observed between medicated and non-medicated groups in the ADHD Rating Scale-IV (ADHD-RS-IV) and Conners Parent Rating Scale. No significant difference was observed in changes in YMRS and CDRS-R scores.

Zeni et al.[11] conducted a randomized crossover trial of methylphenidate and placebo (2 weeks each) in children and adolescents with BD/ADHD previously stabilized with aripiprazole (n=16; age 8-17 years). No significant differences between the effects of methylphenidate and placebo were detected in ADHD ($p = 0.97$) or manic ($p = 0.34$) symptoms. Significant improvement in depressive symptoms was observed in the methylphenidate group ($p = 0.01$). One patient discontinued the trial due to the onset of a severe mixed episode. No other significant adverse events were observed.

Open-label studies

Twelve patients (age 6-17 years) with BD/ADHD underwent an 8-week open trial of atomoxetine combined with at least one mood stabilizer or antipsychotic.[66] A significant decrease in ADHD-RS-IV scores was observed, with no significant changes in YMRS or CDRS-R scored. Response ($\geqslant$ 25% decrease in the ADHD-RS-IV) was seen in eight subjects (67%) and remission ($\geqslant$ 40% decrease in the ADHD-RS-IV), in six patients (50%). Two subjects discontinued early due to worsening of mood symptoms. Placebo-controlled studies are needed to clarify the role of atomoxetine in this population.

Treatment of comorbid BD/ADHD has been understudied. The current evidence suggests the addition of a stimulant (MAS or methylphenidate) or atomoxetine after mood stabilization. Methylphenidate does not seem to be effective in reducing ADHD symptoms when combined with aripiprazole. Although all agents were safe and well tolerated and mood destabilization is the exception rather than the rule, caution is still warranted when introducing stimulants and/or atomoxetine to the therapeutic regimen.

Discussion

Research into the treatment of BD in children and adolescents has increased in recent years, especially regarding the use of SGAs. However, many uncertainties remain. Current algorithms suggest starting with monotherapy and then progressing to combination treatment with two different classes of drugs.[67] Data from RPCTs of traditional mood stabilizers are scarce. The efficacy of some atypical antipsychotic agents (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) has been well demonstrated, especially for aripiprazole and risperidone. Aripiprazole showed efficacy in at least two published RCTs.[25,26] Risperidone also showed higher efficacy than divalproex sodium in two different studies.[20,21] Although no specific SGA has proved to be more effective than others, available meta-analyses and comparative studies of RPCTs suggest that SGAs are more effective than traditional mood stabilizers. Furthermore, a head-to-head comparison of risperidone vs. lithium and divalproex showed that risperidone was superior in terms of efficacy, but with more metabolic side effects.[21] No RPCTs of paliperidone, quetiapine, or ziprasidone have been published to date, and there are no large studies evaluating clozapine in children and adolescents, except for case series. In clinical practice, clozapine is reserved for treatment-refractory cases because of its side effect profile; hence, investigations with greater methodological robustness are required.

Often, children and adolescents with BD trial several medications unsuccessfully before achieving proper mood stabilization.[13] A study of children and adolescents with BD from community samples showed that patients were treated, on average, with 3.4 ± 1.5 medications and had received approximately 6.3 ± 3.7 psychotropic drugs previously.[68,69] Combination therapy is common, and combinations of SGAs are becoming particularly more frequent. A study by the Florida Mental Health Institute evaluating the medical records of 12,764 children (484 of them diagnosed with BD) and 10,419 adolescents (823 of them diagnosed with BD) on Florida Medicaid over 5 years showed that 7% of children and 8% of adolescents were using more than one antipsychotic drug, although evidence indicating the efficacy of antipsychotic combinations in children with BD is limited to reviews of medical records.[70,71] Some data from studies conducted in adults suggest that the side effects of SGAs may be exacerbated when these drugs are used in combination.[72] Based on this information, we believe that combination antipsychotic therapy should be reserved for cases where patients had multiple failures on several different trials of monotherapy, including clozapine. Controlled studies on polypharmacy of antipsychotics in PBD are needed to determine the risk-benefit ratio of this treatment option.

Each drug should be trialed for a sufficient time and at a sufficient dosage to determine the effectiveness of the agent. Generally, a 6- to 8-week course of an antimanic agent, at appropriate doses, is recommended before adding or replacing it with another drug.[5,73-75]

The lack of replication of results of RPCTs and the lack of head-to-head comparisons of different psychopharmacologic approaches precludes the designation of any therapeutic option as having stronger evidence supporting its use in the treatment of BD in children. However, it bears stressing that, in Brazil, the only drugs provided through the national Unified Health System (SUS) are lithium, carbamazepine, and valproate. The effect of lithium has not been adequately studied in RPCTs of

PBD. Studies of valproate suggest it is no different from placebo, and no RPCT is available for carbamazepine. The only comparison of these agents vs. risperidone found that risperidone was more effective than either lithium or valproate. Despite greater documented efficacy (except for paliperidone and clozapine), SGAs are not provided by the government for the treatment of BD, being reserved for proven cases of schizophrenia. This further limits the choice of the most suitable drugs for treatment of pediatric patients with BD. We suggest that risperidone and aripiprazole be included in SUS formularies as a standard treatment for PBD, due to the level of evidence in support of their efficacy and their risk-benefit profile. The cost of other SGAs, which limits their accessibility for most of the population, adds significant and unnecessary suffering and impairment for children, adolescents, and their families. We hope that future Brazilian guidelines include evidence-based treatment for these patients.

Disclosure

Tatiana Lauxen Peruzzolo reports no conflicts of interest. Silzá Tramontina has been a member of the speakers' board for Abbott. Luis Augusto Rohde has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, and Shire in the last 3 years. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him has received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Cristian Patrick Zeni's work is funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

1 Thomas T, Stansifer L, Findling RL. Psychopharmacology of pediatric bipolar disorders in children and adolescents. Pediatr Clin N Am. 2011;58:173-87.
2 Freeman AJ, Youngstrom EA, Michalak E, Siegel R, Meyers OI, Findling RL. Quality of life in pediatric bipolar disorder. Pediatrics. 2009;123:e446-52.
3 Goldstein TR, Birmaher B, Axelson D, Goldstein BI, Gill MK, Esposito-Smythers C, et al. Psychosocial functioning among bipolar youth. J Affect Disord. 2009;114:174-83.
4 Goldstein TR. Suicidality in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009;18:339-52.
5 McClellan J, Kowatch R, Findling RL, Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:107-25.
6 Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2011;50:749-62.
7 Jerrell JM, McIntyre RS, Tripathi A. Childhood treatment with psychotropic medication and development of comorbid medical conditions in adolescent-onset bipolar disorder. Hum Psychopharmacol. 2011;26:451-9.
8 Tramontina S, Schmitz M, Polackzyk G, Rohde LA. Juvenile bipolar disorder in Brazil: clinical and treatment findings. Biol Psychiatry. 2003;53:1043-9.
9 Rohde LA, Tramontina S. O tratamento farmacológico do transtorno bipolar na infância e adolescência. Rev Psiq Clin. 2005;32;117-27.
10 Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry. 1997;36:1378-87.
11 Zeni CP, Tramontina S, Ketzer CR, Pheula GF, Rohde LA. Methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder: a randomized crossover trial. J Child Adolesc Psychopharmacol. 2009;19:553-61.
12 Consoli A, Bouzamondo A, Guilé JM, Lechat P, Cohen D. Comorbidity with ADHD decreases response to pharmacotherapy in children and adolescents with acute mania: evidence from a meta-analysis. Can J Psychiatry. 2007;52:323-8.
13 Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry. 1998;37:171-8.
14 Kowatch RA, Findling RL, Scheffer RE, Stanford KE. Placebo-controlled trial of divalproex vs. lithium for bipolar disorder [poster]. American Academy of Child and Adolescent Psychiatry Annual Meeting; 2007 Oct 23-26; Boston, Massachusetts, USA.
15 Wagner KD, Redden L, Kowatch RA, Wilens TE, Segal S, Chang K, et al. A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2009;48:519-32.
16 Pavuluri MN, Henry DB, Findling RL, Parnes S, Carbray JA, Mohammed T, et al. Double-blind randomized trial of risperidone vs. divalproex in pediatric bipolar disorder. Bipolar Disord. 2010;12:593-605.
17 DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002;41:1216-23.
18 Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, et al. A double-blind, randomized, placebo controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry. 2006;163:1179-86.
19 Delbello MP, Findling RL, Kushner S, Wang D, Olson WH, Capece JA, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:539-47.
20 Haas M, Delbello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009:11:687-700.
21 Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry. 2012;69:515-28.
22 Tohen M, Kryshanovs kaya L, Carlson G, Delbello M, Wosniak J, Kowatch R, et al. Olanzapine vs. placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry. 2007;164:1547-56.
23 U.S. Food and Drug Administration. Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting; 2009 Jun 9-10. [cited 2009 May 12] http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/psychopharmacologicdrugsadvisorycommittee/ucm164280.pdf
24 U.S. Food and Drug Administration. Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting; 2009 Jun 9-10 [cited 2009 May 4] http://www.fda.gov/downloads/AdvisoryCommittees/Committees-MeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisory-Committee/UCM170736.pdf
25 Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2009;70:1441-51.
26 Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. J Clin Psychiatry. 2009;70:756-64.

27 Gracious BL, Chirieac MC, Costescu S, Finucane TL, Youngstrom EA, Hibbeln JR. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disord. 2010;12:142-54.
28 Biederman J, Petty CR, Woodworth KY, Lomedico A, O'Connor KB, Wozniak J, et al. How informative are open-label studies for youth with bipolar disorder? A meta-analysis comparing open-label vs. randomized, placebo-controlled clinical trials. J Clin Psychiatry. 2012;73:358-65.
29 Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2011;50:749-62.
30 McClellan JM. Olanzapine and pediatric bipolar disorder: evidence for efficacy and safety concerns. Am J Psychiatry. 2007;164:1462-4.
31 Nandagopal JJ, DelBello MP. Pharmacotherapy for Pediatric Bipolar Disord Psychiatric Ann. 2010;40:221-30.
32 Potter M, Moses A, Wozniak J. Alternative treatments in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009;18: 483-514.
33 DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disord. 2009;11:483-93.
34 Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM. Lithium treatment of acute mania in adolescents: a placebo controlled discontinuation study. J Am Acad Child Adolesc Psychiatry. 2004;43:984-93.
35 Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, et al. Double-blind 18-month trial of lithium vs. divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:409-17.
36 Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. J Clin Psychiatry. 2012;73:57-63.
37 Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry. 2005;162:58-64.
38 Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:1445-53.
39 Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord. 2010;12:116-41.
40 Kafantaris V, Coletti D, Dicker R, Padula G, Kane JM. Lithium treatment of acute mania in adolescents: a large open trial. J Am Acad Child Adolesc Psychiatry. 2003;42:1038-45.
41 Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG. Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. Bipolar Disord. 2005;7:266-73.
42 Wagner KD, Weller EB, Carlson GA, Sachs G, Biederman J, Frazier JA, et al. An open label trial of divalproex in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2002;41:1224-30.
43 Pavuluri MN, Henry DB, Moss M, Mohammed T, Carbray JA, Sweeney JA. Effectiveness of lamotrigine in maintaining symptom control in pediatric bipolar disorder. J Child Adolesc Psychopharmacol. 2009;19:75-82.
44 Biederman J, Joshi G, Mick E, Doyle R, Georgiopoulos A, Hammerness P, et al. A prospective open-label trial of lamotrigine monotherapy in children and adolescents with bipolar disorder. CNS Neurosci Ther. 2010;16:91-102.
45 Biederman J, Mick E, Wozniak J, Aleardi M, Spencer T, Faraone SV. An open-label trial of risperidone in children and adolescents with bipolar disorder. J Child Adolesc Psychopharmacol. 2005;15:311-7.
46 Frazier JA, Biederman J, Tohen M, Feldman PD, Jacobs TG, Toma V, et al. A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. J Child Adolesc Psychopharmacol. 2001;11:239-50.
47 Marchand WR, Wirth L, Simon C. Quetiapine adjunctive and monotherapy for pediatric bipolar disorder: a retrospective chart review. J Child Adolesc Psychopharmacol. 2004;14:405-11.
48 Biederman J, Mick E, Spencer T, Dougherty M, Aleardi M, Wozniak J. A prospective open-label treatment trial of ziprasidone monotherapy in children and adolescents with bipolar disorder. Bipolar Disord. 2007;9:888-94.
49 Tramontina S, Zeni CP, Pheula GF, de Souza CK, Rohde LA. Aripiprazole in juvenile bipolar disorder comorbid with attention-deficit/hyperactivity disorder: an open clinical trial. CNS Spectr. 2007;12:758-62.
50 Findling RL, McNamara NK, Youngstrom EA, Stansbrey RJ, Frazier TW, Lingler J, et al. An open-label study of aripiprazole in children with a bipolar disorder. J Child Adolesc Psychopharmacol. 2011;21:345-51.
51 Pavuluri MN, Henry DB, Carbray JA, Sampson GA, Naylor MW, Janicak PG. A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. J Child Adolesc Psychopharmacol. 2006;16:336-50.
52 Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG. Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. J Affect Disord. 2004;82:S103-11.
53 Biederman J, Mick E, Hammernessa P, Harpold T, Aleardi M, Dougherty M, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. Biol Psychiatry. 2005;58:589-94.
54 Wozniak J, Mick E, Waxmonsky J, Kotarski M, Hantsoo L, Biederman J. Comparison of open-label, 8-week trials of olanzapine monotherapy and topiramate augmentation of olanzapine for the treatment of pediatric bipolar disorder. J Child Adolesc Psychopharmacol. 2009;19:539-45.
55 Masi G, Mucci M, Millepiedi S. Clozapine in adolescent inpatients with acute mania. J Child Adolesc Psychopharmacol. 2002;12:93-9.
56 Wozniak J, Biederman J, Mick E, Waxmonsky J, Hantsoo L, Best C, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. Eur Neuropsychopharmacol. 2007;17:440-7.
57 Rucklidge JJ, Gately D, Kaplan BJ. Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. BMC Psychiatry. 2010;10:74.
58 Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, et al. Effect size of lithium, divalproex sodium and carbamazepine in children and adolescent with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2000;39:713-20.
59 Joshi G, Wozniak J, Mick E, Doyle R, Hammerness P, Georgiopoulos A, et al. A prospective open-label trial of extended-release carbamazepine monotherapy in children with bipolar disorder. J Child Adolesc Psychopharmacol. 2010;20:7-14.
60 Patel NC, DelBello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, et al. Open-label lithium for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry. 2006;45:289-97.
61 Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry. 2006;45:298-304.
62 Biederman J, Mick E, Spencer TJ, Wilens TE, Faraone SV. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. J Child Adolesc Psychopharmacol. 2000;10:185-92.
63 Findling RL, McNamara NK, Stansbrey R, Gracious BL, Whipkey RE, Demeter CA, et al. Combination lithium and divalproex sodium in pediatric bipolar symptom restabilization. J Am Acad Child Adolesc Psychiatry. 2006;45:142-8.
64 Tramontina S, Zeni CP, Pheula G, Rohde LA. Topiramate in adolescents with juvenile bipolar disorder presenting weight gain due to atypical antipsychotics or mood stabilizers: an open clinical trial. J Child Adolesc Psychopharmacol. 2007;17:129-34.
65 Duffy A, Milin R, Grof P. Maintenance treatment of adolescent bipolar disorder: open study of the effectiveness and tolerability of quetiapine. BMC Psychiatry. 2009;9:4.
66 Chang K, Nayar D, Howe M, Rana M. Atomoxetine as an adjunct therapy in the treatment of co-morbid attention-deficit/hyperactivity

disorder in children and adolescents with bipolar I or II disorder. J Child Adolesc Psychopharmacol. 2009;19:547-51.
67 Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M, et al. Treatment guidelines for children and adolescents with bipolar disorder: child psychiatric workgroup on bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:213-35.
68 Duffy FF, Narrow WE, Rae DS, West JC, Zarin DA, Rubio-Stipec M, Pincus HA, et al. Concomitant pharmacotherapy among youths treated in routine psychiatric practice. J Child Adolesc Psychopharmacol. 2005;15:12-25.
69 Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state medicaid program. Cli Ther. 2010;32:949-59.
70 Drug Use Research & Management Program from the College of Pharmacy of the Oregon State University. Drug use evaluation: duplicate atypical antipsychotics. 2007. http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/dup_app.pdf
71 Nandagopal JJ, DelBello MP, Kowatch R. Pharmacologic treatment of pediatric bipolar disorder. Child Adolesc Psychiatric Clin N Am. 2009;18:455-69.
72 Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. Curr Med Chem. 2004;11:313-27.
73 Fraguas D, Correll CU, Merchán-Naranjo J, Rapado-Castro M, Parellada M, Moreno C, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. Eur Neuropsychopharmacol. 2011;21:621-45.
74 Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 2005;44:846-71.
75 McClellan J, Kowatch R, Findling RL, Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:107-25.