REVIEW

Empirical Evidence for the Use of Lithium and Anticonvulsants in Children with Psychiatric Disorders

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***Background*: The use of psychotropic medications—in particular, mood stabilizers—in youths with psychiatric illness has grown. There are trends toward polypharmacy and the increased use of newer mood stabilizers in youths with psychiatric illness despite a paucity of studies examining the short- and long-term efficacy and safety of these agents in the pediatric population. *Method*: PubMed was used to identify peer-reviewed publications from the past 30 years (January 1975 to August 2005) studying lithium and anticonvulsants in youths with psychiatric illness. *Results*: Evidence supporting the use of lithium and valproate in the treatment of juvenile bipolar disorder and reactive aggression has grown. Evidence for the use of other anticonvulsants in youths with psychiatric illness is sparse. Side effects from lithium and anticonvulsants are typically mild to moderate. Data are accumulating in regard to the longer-term safety of lithium and DVPX in the juvenile psychiatric population. Although data in regard to the newer anticonvulsants are limited, they may have more desirable side-effect profiles. *Conclusion*: Double-blind, placebo-controlled trials of lithium and anticonvulsants are greatly needed as clinical use of these agents has risen without sufficient evidence supporting their efficacy in the pediatric population. (HARV REV PSYCHIATRY 2006;14:285–304.)**

Keywords: aggression, bipolar disorder, carbamazepine, children and adolescents, gabapentin, lamotrigine, lithium, oxcarbazepine, topiramate, valproate

INTRODUCTION

Over the past eight to ten years, there has been an increase in the use of psychotropic medications in youths with psychiatric illness.[1,2] For example, a study examining the use of psychotropic medications in a child psychiatric hospital reported a 73% increase in prescriptive practice from 1991 to 1998, with the clinical use of mood stabilizers changing from 14.9% to 32.6%.[2] There was a marked rise in valproate (DVPX) use, from 1.8% to 24.5%, and a decline in carbamazepine (CBZ) use, from 7.7% to 3.9%. Lithium use remained stable, falling slightly from 5.4% to 4.2%. According to a study of inpatient prescribing practices in children 9 years of age and younger, the most common reason for hospitalization was for behavioral disorders, with mood disorders being the next largest category.[1] The youths with behavioral disorders were more likely to be on more than one medication at both admission and discharge. Bhangoo and associates[3] looked at medication use in the community among children and adolescents with bipolar disorder (BPD), and found that youths were treated with an average of 3.4 (SD = 1.5) medications and had an average of 6.3 (SD = 3.7) prior medication trials. Ninety-eight percent of youths with BPD had a mood stabilizer trial, with the most common being DVPX (79%), followed by lithium (51%) and

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gabapentin (29%). Fifteen percent of these youths had a trial of gabapentin, lamotrigine, or topiramate, but had not had a trial of lithium. The growing use of mood stabilizers, with trends toward polypharmacy and the increased use of newer mood stabilizers in youths, is notable in view of the paucity of studies examining the short- and long-term efficacy and safety of these agents in the pediatric population. Evidence is growing, however, to support the use of mood stabilizers in certain psychiatric conditions. The purpose of this article is to review the current literature regarding the efficacy and safety of lithium and anticonvulsants in youths with psychiatric disorders, with an emphasis on larger prospective and double-blind, placebo-controlled trials when available; otherwise, retrospective and case series and reports are included. The scope of this review will be limited to lithium and anticonvulsants unless concomitant pharmacotherapy was evaluated in the study. Although atypical antipsychotics have been described as "mood stabilizers," this term will refer only to lithium and anticonvulsants in this review. For a comprehensive review of the use of atypical antipsychotics in children and adolescents with psychiatric illness, see a report by Findling and associates.[4]

METHODS

Computerized searches were performed with PubMed from 1975 to 2005. Keywords included aggression, bipolar disorder, carbamazepine, children and adolescents, conduct disorder, depression, gabapentin, lamotrigine, lithium, mood stabilizer, oppositional defiant disorder, oxcarbazepine, pervasive developmental delay, topiramate, and valproate. The searches were limited to English, human subjects, and subjects $\leq$18 years of age. We selected, when available, controlled studies and open trials conducted on at least ten subjects. Only placebo-controlled trials and large prospective trials are displayed in the tables unless a smaller study contributed substantially to the literature.

RESULTS

Bipolar Disorder

The prevalence of BPD in youths is similar to that of adults and is estimated to be 1% of the population.[5] Juvenile BPD is a severe, chronic, and impairing illness with a poor prognosis. The presence of mixed states and rapid cycling in juvenile BPD—complicated by high rates of suicidality, psychosis, and comorbidity, particularly attention-deficit/hyperactivity disorder (ADHD)[6–9]—makes diagnosis difficult and often necessitates the use of a thoughtful, multidrug regimen. Mood stabilizers, particularly lithium and DVPX, have been suggested as first-line treatments for youths with BPD.[10] Despite the controversy and diagnostic difficulties surrounding the diagnosis of juvenile BPD, insight into the optimal treatment of this severely ill population is greatly needed.

Lithium Monotherapy. In a double-blind, placebo-controlled trial of lithium treatment in adolescents with BPD and secondary substance dependence, Geller and associates[11] found lithium to be an effective treatment for both disorders. This outpatient study involved 25 adolescents with BPD and comorbid substance dependence who were prescribed either lithium or placebo over a 6-week period. Significant improvement in the Children's Global Assessment Scale (CGAS) (a response defined as CGAS $>$ 65) was found in the lithium-treated youths compared to the placebo-treated youths, along with intent-to-treat and completer response rates of 46% and 60%, respectively, in the lithium group, compared to 8% and 9% in the placebo group. There were no significant differences, however, between the active and placebo groups on the K-SADS-1986 (Schedule for Affective Disorders and Schizophrenia for School-Age Children) mood items or on the substance-dependence items (nine items from the DSM-III criteria for substance dependence disorder).[11] Similar response rates (ranging from 42% to 68%) have been reported in several prospective, open-label lithium trials in youths with BPD,[9,12–14] mirroring the response rates reported in adults with BPD.[15] In a 4-week, mostly inpatient, open-label lithium trial in 100 youths with BPD, Kafantaris and associates[9] reported a response rate of 63% (55% using strict criteria) and a remission rate of 26%. Response was defined using the Clinical Global Impressions Improvement (CGI) score of 1 ("very much improved") or 2 ("much improved"), plus a decline in the Young Mania Rating Scale score (YMRS) of $\geq$33% (or $\geq$50% using more strict criteria). Remission was defined as a YMRS score $\leq$6. A large effect size for the change in manic symptoms of 1.48 was reported. The response rates were not found to be associated with baseline psychosis (when adjunctive antipsychotic medication was used, the response rate was 65.7%), depressive symptoms, comorbid ADHD, early onset, severity, or hospitalization. Suicidal ideation was reduced in 19 out of 23 youths. (Notably, antisuicidal effects of lithium have also been reported in adults with BPD.)[16,17] One of the limitations of the study by Kafantaris and associates[9] was the use of adjunctive antipsychotic agents (46 %), making it difficult to assess the efficacy of lithium alone. In another study of 50 hospitalized adolescents with BPD, response rates of lithium treatment were 56% at 4 weeks and 68% at 6 weeks; again, however, the use of adjunctive antipsychotic agents confounded these results.[12]

In an 18-month, naturalistic, prospective, follow-up study of 37 adolescents who had been stabilized on lithium, there was nearly triple the relapse rate in those who discontinued (92%) versus those who continued (38%) on lithium,

suggesting it is effective in the maintenance treatment of juvenile BPD.[18] The authors also reported that among those youths who had prior affective episodes, there was a greater decline in the number of subsequent relapses among study completers than among noncompleters.[18] A placebo-controlled discontinuation trial of lithium treatment of acute mania in adolescents with BPD found that exacerbation rates for lithium and placebo were similar—52.6% and 61.9%, respectively.[19] The authors note that their findings were unexpected and offer several explanations for the high exacerbation rates in the lithium-treated group, including: (1) use of subjective reporting of deterioration rather than objective numerical criteria, (2) low threshold for measuring exacerbation of symptoms that may have been only transient in nature, (3) a short stabilization period, and (4) psychosocial stressors (since some patients were discharged home during the study).

Age of illness onset, the presence of mixed states, and comorbidities may complicate lithium response. For example, poor or partial lithium response has been reported in two independent prospective trials by Strober and associates,[12] who found a lithium response rate (CGI of 1 or 2) of 40% in prepubertal-onset BPD (onset of any Axis I disorder before the age of 12), versus an 80% response rate in adolescent-onset BPD, and a 33% response rate (CGI = 1) in adolescents with a history of ADHD, versus a 66.7% response rate in youths without a history of ADHD.[13] However, poor lithium response in early-onset BPD and in comorbid ADHD have not been reported in other studies.[9,14] In one open-label study of 10 prepubertal, hospitalized children with BPD with acute mania and psychotic features, the children showed significant improvement (including resolution of psychotic symptoms) on lithium monotherapy alone,[20] but the presence of psychosis has been more lithium refractory, requiring adjunctive antipsychotic treatment in studies of adolescents with BPD.[21–23] With adjunctive antipsychotic treatment, the response rate (65%) in youths with BPD and psychotic features has been reported to be similar to that in youths with BPD without psychosis.[9] A reduction in lithium response has also been reported in youths with mixed states.[24]

In summary, the data suggesting the effectiveness of lithium for the acute and maintenance treatment of juvenile BPD comes from one placebo-controlled trial and several open-label trials (see Table 1). Lithium may protective against suicidality and relapse, and may reduce the frequency of future affective episodes. Furthermore, poor or partial lithium response has been associated with age of illness onset, mixed status, and presence of ADHD or psychosis in some, but not all, studies.

Valproate Monotherapy. Small, open-label trials of DVPX support its efficacy in the treatment of youths with BPD.[25–27] West and associates[25] reported a study of 11 hospitalized adolescents with acute mania who were nonresponders to lithium and antipsychotics, and found at least a moderate therapeutic response when the patients were treated with open-label DVPX. In addition, in a 7-week open trial of 15 acutely manic adolescents treated with DVPX, 80% reported at least 50% improvement in manic symptoms.[26] Unfortunately, both of these studies used adjunctive agents, making it difficult to assess the efficacy of DVPX alone.[25,26] Wagner and colleagues[28] conducted a 2- to 8-week open trial of DVPX monotherapy in 40 youths with BPD, followed by a double-blind, placebo-controlled, discontinuation phase for responders ($n = 17$). The authors reported a response rate of 61%, where response was defined as a $\geq$50% decline in Mania Rating Scale (MRS) scores from baseline, which yielded a large effect size of 1.12.[28] Significant reductions were also noted for the Brief Psychiatric Rating Scale, CGI-Severity scale, and Hamilton Rating Scale for Depression (HAM-D) in the open trial, although 53% of participants required adjunctive medications. Response was rapid, with improvement noted in the first week. Unfortunately, 58% prematurely discontinued the open-label portion of the study, and 82% (14 of 17) prematurely discontinued the double-blind portion (with lack of efficacy being the most common reason for early withdrawal), thus leaving too few participants to analyze the study's double-blind phase. Furthermore, in a 6-week, open-label comparison trial of several mood stabilizers in youths with BPD, DVPX was found to have a response rate of 46% and a large effect size of 1.63.[14] In a 6-month, open-label, prospective trial of DVPX in youths with BPD with a current mixed presentation, a 73.5% response rate (YMRS $\geq$50% from baseline and Child Depression Rating Scale–Revised [CDRS-R] score $\leq$40) and a remission rate of 52.9% (YMRS $\geq$ 50% from baseline, CDRS-R $\leq$ 40, CGI-I $\leq$ 2, and CGAS $\geq$ 51) were reported.[29] The strengths of this study were its length and its homogenous patient population, since all youths were in mixed states. Finally, Chang and associates[30] performed a 12-week, open, DVPX monotherapy trial in BPD offspring with mood and behavioral disorders who did not yet meet criteria for BPD I or II.[30] The authors reported response rates of 78% by primary (CGI-I of 1 or 2) and 83% by secondary (YMRS or HAM-D $\geq$ 50%) criteria.

Evidence for the use of DVPX in the acute treatment of juvenile BPD comes primarily from several open-label, prospective trials (see Table 2). DVPX has shown promise in reducing mood and behavioral symptoms in youths with strong family histories of BPD and in treating youths in mixed states. These findings strongly support the need for randomized, placebo-controlled DVPX trials in youths with BPD.

Comparison Studies. DVPX has been shown to be more effective than lithium in the treatment of mixed states and rapid

TABLE 1. Select Studies of Lithium Treatment in Juvenile Bipolar Disorder

	Design	Entry criteria/age (mean)	Target serum level; dose; mean serum level achieved	*N* at entry/ retained	Outcome measures	Concurrent medications	Definition of outcome/efficacy results
Lithium monotherapy							
Strober et al. (1988)[12]	6-wk, open-label, in-hospital, prospective, naturalistic Li+ trial	DSM-III BPD, manic; age 13–17	Target, 0.9–1.5 mEq/L	50 (15, prepubertal onset; 35, adolescent onset)	BHS, MSRS, CGI Response: CGI ≤ 2	Antipsychotics	68% response rate at 6wks (80%, adolescent onset; 40%, prepubertal onset)* 13/15 prepubertal-onset adolescents had comorbid ADHD
Strober et al. (1990)[18]	18-mo, prospective, follow-up Li+ maintenance study	DSM-III BPD I, manic; RSMS ≥ 7; BHS ≥ 8; age 13–17 (mean, 15.1)	Target, 0.6–1.2 mEq/L; achieved, 0.7–1.4 mEq/L (at stabilization), 0.79 mEq/L (completers at end of 18 mo)	37 enrolled 24 completed	Stable: RSMS ≤ 5; HAM-D ≤ 7; ↓BHS ≥ 50%; ↓MSRS ≥ 50%; CGI ≤ 2 for 4 wk Relapse/exacerbation: MDD or mania	Antipsychotics Carbamazepine	56.8% relapse rate (3× higher in noncompleters [92.3%] than in completers [37.5%])* Relapses clustered in first 12 months; subsequent decline in no. of episodes in lithium completers who had prior episodes
Strober et al. (1998)[13]	4-wk, open, prospective trial of Li+ in hospitalized adolescents w/ and w/o Hx ADHD	DSM-III-R or DSM-IV manic w/ Hx ADHD; age 13–17	Target, 0.9–1.5 mEq/L; achieved (mean), 1.12 mEq/L	60 (30 w/, 30 w/o ADHD)	BRMS, CGI Response: CGI ≤ 2 or ↓BRMS ≥ 50%	Antipsychotics	At 4 wk, 86.7% of non-ADHD and 66.7% of ADHD patients responded (difference not significant) Using CGI of 1 to define response, 66.7% of non-ADHD vs. 33.3% of ADHD patients responded*
Geller et al. (1998)[11]	6-wk, double-blind, placebo-controlled, outpatient study of Li+ in BPD and SDD	DSM-III-R SDD and BPD I/II, manic or depressed; age 12–18 (16.3 ± 1.2)	Target, 0.9–1.3 mEq/L; dose, 1769 ± 401 mg/d; achieved, 0.98 ± 0.33 mEq/L	25 enrolled (13, Li+; 12, placebo) 21 completed	CGAS Response: CGAS ≥ 65		Intent-to-treat response: 46.2% for Li+ vs. 8.3% for placebo* Completer response: 60% for Li+ vs. 9.1% for placebo* No significant difference between groups for mood or SDD symptoms
Kafantaris et al. (2003)[9]	4-wk, open-label, prospective trial of Li+; 77% inpatient	DSM-IV BPD I, current manic or mixed episode; YMRS ≥ 16; age 12–18 (15.2 ± 1.9)	Target, 0.6–1.2 mEq/L; dose, 1355 ± 389 mg/d; achieved, 0.93 ± 0.21 mEq/L	100 enrolled	YMRS, HAM-D, BPRS, CGI, CGAS Response: ↓YMRS > 33% (strict ≥50%) and CGI ≤ 2 Remission: YMRS ≤ 6	Antipsychotics (46%) Benzodiazepines	63% response rate (strict, 55%); 26% achieved remission of manic symptoms; 19 of 23, reduction in suicidality Effect Size: YMRS, 1.48; CGAS, 1.21; CGI, 1.40
Kafantaris et al. (2004)[19] (extension of Kafantaris et al. 2003)[9]	2-wk, double-blind, placebo-controlled, discontinuation study of Li+ in acute mania	DSM-IV current manic episode; YMRS ≥ 16; age 12–18 (15.2 ± 1.7)	Target, 0.6–1.2 mEq/L; achieved, 0.99 ± 0.21 (at randomization)	100 enrolled 45 responders 40 randomized (19, Li+; 21, placebo)	Exacerbation: "moderately or markedly worse" on CGI, or requiring a more restrictive treatment setting	Antipsychotics (25%) Benztropine Benzodiazepines	20% response rate in those w/ psychotic or aggressive symptoms, vs. 60.3% response rate for those w/o* Exacerbation rate for Li+ (52.6%) and placebo (61.9%) were similar
Lithium and adjunctive agent							
Kafantaris et al. (2001)[22]	4-wk, prospective, open-label trial of combination Li+ w/ antipsychotic	DSM-IV BPD I, current manic or mixed w/ psychotic features; YMRS ≥ 16; age 12–18 (15.95 ± 1.92)	Li+: target, 0.6–1.2 mEq/L HAL: dose, 5–10 mg/d RIS: dose, ≤6 mg/d	35 enrolled 28 completed 4 wks (14, trial of Li+ monotherapy)	YMRS, BPRS, Ham-D, CGI, CGAS Responders: ↓YMRS > 33% and CGI ≤ 2 Remission: YMRS ≤ 6	Lorazepam Benzodiazepines	64.3% responded to combination treatment; 57% stable on monotherapy for 4 wks Differences between groups were found for duration of index psychotic episode, prior treatment history, and first episode of psychosis*

Kowatch et al. (2003)[33] (extension phase of Kowatch et al. 2000)[14]	6-mo, prospective, semi-naturalistic study w/ 6–8 wks of acute monotherapy w/ mood stabilizer, followed by 16 wk of open treatment	DSM-IV BPD I or II, mixed, manic or hypomanic; YMRS $\geq$ 14 at entry of acute phase; age 7–18 (11 $\pm$ 2.8)	Li+: target, 0.8–1.2 mEq/L; dose, 30 mg/kg/d; achieved, 0.88 $\pm$ 0.35 mEq/L DPVX: target, 85–110 μg/ml; dose, 20 mg/kg/d; achieved, 82.8 $\pm$ 22.92 μg/ml CBZ: target, 7–10 μg/L; dose, 15 mg/kg/d; achieved, 7.11 $\pm$ 1.79 μg/L	35 subjects 18 acute-phase responders 17 acute phase nonresponders	CGI, YMRS Response: CGI $\leq$ 2 or $\downarrow$YMRS $\geq$ 50%	Mood stabilizers Antidepressants Antipsychotics Stimulants	58% required 1 or 2 mood stabs. + either a stim, SGA, or antidepressant 80 response rate w/ combination treatment 5 nonresponders at end of study
Findling et al. (2003)[23]	Up to 20-wk, prospective, open-label trial of combination Li+ w/ DVPX	DSM-IV BPD I or II, hypomanic, manic, mixed, depressed, euthymic; age 5–17 (mean 10.9 $\pm$ 3.4)	Li+: target, 0.6–1.2 mEq/L; dose, 30 mg/kg/d (923.3 $\pm$ 380.2 mg/d); achieved, 0.9 $\pm$ 0.3 mEq/L DVPX: target, 50–100 μg/ml; dose, 20 mg/kg/d (862.5 $\pm$ 397.5 mg/d); achieved, 79.8 $\pm$ 25.9 μg/ml	90 subjects	CDRS-R, YMRS, CGI, CGAS Response: $\downarrow$YMRS $\geq$ 50% or CGI $\leq$ 2 Remission: CDRS-R $\leq$ 40; YMRS $\leq$ 12.5; and CGAS $\geq$ 51 for 4 wk	Stimulants (59%) α2agonist (24%) Antipsychotics (21%) Antidepressants (11%)	70.6% (YMRS) and 59.3% (CGI) response rates at 8 wk 46.7% met criteria for remission; lifetime history of psychosis or presence of psychosis at baseline was more common in nonremitters
Pavuluri et al. (2004)[35]	6-mo, open-label, prospective trial of combination therapy: RIS w/ Li+ vs. RIS w/ DVPX	DSM-IV BPD I, mixed or manic; YMRS > 20; age 5–18 (12.1 $\pm$ 3.5)	RIS: target, 0.25–0.50 mg/d to max 3 mg/d (w/ Li+, 0.75 $\pm$ 0.75 mg/d; w/ DPVX, 0.70 $\pm$ 0.67 mg/d) Li+: target, 0.6–1.0 mEq/L; dose, 10–30 mg/kg/d (750 $\pm$ 400 mg/d); achieved (mean), 0.9 mEq/L DPVX: target, 50–120 μg/mL; dose, 15–20 mg/kg/d (925 $\pm$ 325 mg/d); achieved (mean), 106 μg/mL	40 enrolled 37 completed at least one month	YMRS, CDRS-R, CGI, CGAS Response: $\downarrow$YMRS $\geq$ 50% Remission: $\downarrow$YMRS $\geq$ 50%; CGI $\leq$ 2; and CGAS $\geq$ 51	Stimulants (8%) Benztropine (8%) Clonidine (14%) Trazodone (16%)	YMRS response rate of 80% for RIS + DVPX, 82.4% for RIS + Li+; also significant improvement on secondary measures (60–74.7%);* no significant differences between treatment groups Remission rate of 64.7% for Li + RIS, 60% for DVPX + RIS; effect size of 2.82 for Li + RIS, 4.36 for DVPX + RIS

ADHD, attention-deficit/hyperactivity disorder; BHS, Bunney-Hamburg Scale of manic severity; BPD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; BRMS, Bech-Rafaelsen Mania Scale; CDRS-R, Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; CGI, Clincial Global Impressions Improvement (1, very much improved; 2, much improved); DVPX, valproate; HAL, haloperidol; HAM-D, Hamilton Rating Scale for Depression; Li+, lithium; Hx, history; MDD, major depressive disorder; MSRS, Manic State Rating Scale; RIS, risperidone; RSMS, Raskin Severity of Mania Scale; SDD, substance dependence disorder; YMRS, Young Mania Rating Scale.

*Statistically significant at $p < 0.05$.

TABLE 2. Select Studies of Valproate Treatment in Juvenile Bipolar Disorder

	Design	Entry criteria/age (mean)	Target serum level; dose; mean serum level achieved	*N* at entry/ retained	Outcome measures	Concurrent medications	Definition of outcome/efficacy results
Valproate monotherapy							
Wagner et al. (2002)[28]	2- to 8-wk, open trial of DVPX monotherapy followed by double-blind, placebo-controlled, discontinuation phase for responders	BPD I/II, mixed, manic, or hypomanic; age 7–19 (12.1 ± 3.6)	Target, (45–125 μg/mL); dose, 15 mg/kg/d (813 ± 338 mg/d); achieved, 83.4 ± 25.4 μg/mL	Phase 1: 40 Phase 2: 17 3 completed	MRS, BPRS, HAM-D, CGI Response: ↓MRS ≥ 50% Criteria for double-blind entry: CGAS ≥ 51, CGI ≤ 2, MRS ≤ 11, SADS-D ≤ 9	Antipsychotics (20%) Stimulants (15%) Benzodiazepines (18%)	61% response rate in open trial,* although half required other meds Significant reductions from baseline to the final evaluation in all clinical measures* 58% prematurely discontinued open-label portion 82% of double-blind group terminated early, so statistical analysis was not done Effect size: 1.12
Chang et al. (2003)[30]	12-wk, open DVPX trial in BPD offspring with mood and behavioral disorders who did not meet criteria for BPD I or II	At least one parent with DSM-IV BPD I/II + one of the following (DSM-IV): MDD, dysthymic disorder, cyclothymic disorder, ADHD; HAM-D or YMRS >12; age 6–18 (11.3±3.9)	Target, 50–120 μg/mL; dose, 15–20 mg/kg/d (mean, 821 mg/d); achieved, 79.0 ± 26.8μg/mL	24 enrolled (58%, ADHD; 29%, cyclothymia; 21%, MDD; 8%, dysthymia) 23 completed	YMRS, HAM-D, CGI, CBCL, RCMAS Response: CGI ≤ 2; or YMRS or HAM-D ≥ 50%	57% exposure to psychotropic medications, including antidepressants, stimulants, antipsychotics	78% responders by CGI criteria, 83% by YMRS or HAM-D criteria. YMRS and HAM-D scores significantly lower as early as week 2 Nonresponders more likely to be male and have ADHD
Pavuluri et al. (2005)[29]	6-mo, open trial of DVPX monotherapy for BPD	DSM-IV BPD, mixed; YMRS > 20; age 15–18 (12.3 ± 3.7)	Target, 50–120 μg/mL; dose, 15–20 mg/kg/d (950 ± 355 mg/d); achieved, 109 ± 33 μg/mL	35 enrolled 34 completed	YMRS, CDRS, CGI, CGAS Response: YMRS ≥ 50% and CDRS ≤ 40 Remission: response criteria + CGI ≤ 2 and CGAS ≥ 51	Stimulants (38%) Antipsychotics, trazodone (used as rescue meds)	73.5% responded, 52.9% remitters YMRS effect size: 2.9 CDRS effect size: 1.23
Valproate and adjunctive treatment							
DelBello et al. (2002)[34]	6-wk, double-blind, placebo- controlled study of QTP + DVPX	DSM-IV BPD I, current manic or mixed; YMRS ≥ 20; age 12–18	QTP: 450 mg/d DVPX: target, 80–130 mg/dL; dose, 20 mg/kg/d; achieved, 102 mg/dL (monotherapy), 104 mg/dl (combination)	30 (15 in each group)	YMRS, CDRS, PANSS-P, CGAS Response:↓YMRS ≥ 50%	Benzodiazepines	87% response rate for QTP + DVPX* 53% response rate for DVPX monotherapy*

ADHD, attention-deficit/hyperactivity disorder; BPD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CBCL, Children's Behavioral Check List; CDRS, Children's Depression Rating Scale; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impressions; DVPX, valproate; HAM-D, Hamilton Rating Scale for Depression; MDD, major depressive disorder; MRS, Mania Rating Scale; PANSS-P, Positive and Negative Syndrome Scale–positive subscale; RCMAS, Revised Children's Manifest Anxiety Scale; QTP, quetiapine; SADS-D, Schedule for Affective Disorders and Schizophrenia–depressed mood score; YMRS, Young Mania Rating Scale.

*Statistically significant at $p < 0.05$.

cycling in adult patients with BPD,[31] and a recent, 6-month prospective study found that it was effective in the treatment of mixed states in juvenile BPD.[29] Since juvenile BPD is often associated with mixed states and rapid cycling,[6–8] DVPX may be more effective than lithium in the treatment of this disorder. A study performed by Kowatch and associates,[14] however, found that lithium and DVPX were comparable in efficacy. In that study, 42 youths with BPD I or II were randomized to 6 weeks of open treatment with DVPX, lithium, or CBZ. Using a ≥50% reduction from baseline to endpoint YMRS and a CGI ≤ 2 to define response, the mean response rates were 46% for DVPX , 42% for lithium, and 34% for CBZ.[14] There were no significant differences among treatment groups, but a lack of a placebo control arm and a small sample size may have limited the study's ability to detect differences among the three medications.[14] All three agents were found to have a large effect size, which ranged from 1.0 to 1.6, yet only 13 of 42 youths completed 6 weeks, and only 3 youths completed 8 weeks.[14] In a multiphase study performed by Findling and associates,[32] 60 youths with BPD were randomized to receive double-blind maintenance treatment of lithium or DVPX monotherapy for 76 weeks after achieving remission with open-label DVPX-lithium combination treatment. Time to mood relapse and time to discontinuation did not differ between the DVPX- and lithium-treated groups. Youths with a younger age of onset were more likely to relapse, and youths with higher YMRS scores at baseline were more likely to discontinue the study early. Age, comorbid ADHD, rapid-cycling status, gender, duration of illness, baseline CDRS, and concurrent use of ADHD medications were not associated with time until mood event or study discontinuation, and there were no differences between treatment groups on any secondary measure.

These preliminary reports suggest that lithium and DVPX are equally efficacious in the acute and maintenance treatment of juvenile BPD, regardless of the presence of rapid cycling; nevertheless, further studies investigating predictors of response are needed in youths with BPD (see Table 3).

Combination Treatments. Given the high rates of partial or no response to monotherapy treatment and the need for frequent "rescue" medications in monotherapy mood stabilizer trials in youths with BPD, several studies have examined whether response rates are improved with combination treatments. For example, Findling and associates[23] performed a prospective, open-label trial of combination lithium and DVPX treatment for up to 20 weeks and found response rates of 70.6% as measured by a decline in YMRS ≥50% from baseline, and of 59.3% as measured by a CGI ≤ 2), with 47% meeting criteria for remission (CDRS-R ≤ 40, YMRS ≤ 12.5, and CGAS ≥ 51, all for 4 consecutive weeks without the need for adjunctive antidepressants, antipsychotics, or additional mood stabilizers). A lifetime history of psychosis or presence of psychosis at baseline was more common in nonremitters. In two studies performed by Kafantaris and associates[21,22] in adolescents with BPD (either acutely manic or mixed with psychotic features), antipsychotic agents in conjunction with lithium were found to be helpful, and early withdrawal resulted in relapse. In the first study, 5 youths with BPD and prominent psychotic features had their haloperidol discontinued after 1 week of therapeutic lithium levels and resolution of psychotic symptoms. These youths experienced a reemergence of their psychotic symptoms within 1 week after withdrawal of haloperidol.[21] In an extension of this study, Kafantaris and associates[22] performed a 4-week, prospective, open-label trial in 42 adolescents with BPD using lithium in combination with an antipsychotic agent, followed by a trial of lithium monotherapy for responders. Sixty-four percent responded to combination treatment. In the subsequent trial of lithium monotherapy, 8 of 14 (57%) remained stable for 4 weeks, whereas 6 of 14 (43%) had exacerbations of symptoms. In this study, responders were more likely to be medication naive and to be experiencing their first psychotic episodes. Adolescents who had a prior psychotic episode could not tolerate discontinuation of their antipsychotic medication. A 6-month extension study by Kowatch and associates[14,33] followed 35 youths with BPD who had received 6 to 8 weeks of monotherapy with lithium, DVPX, or CBZ. Eighteen youths were acute-phase responders, and 17 were nonresponders.[33] Forty-two percent of the youths were treated with a single mood stabilizer, whereas 58% of the youths required treatment with at least one mood stabilizer plus a stimulant, an atypical antipsychotic agent, or an antidepressant, with a reported response rate of 80% with combination treatment. A 6-week, double-blind, placebo-controlled trial of DVPX monotherapy compared to DVPX-quetiapine (QTP) combination therapy in acutely manic, hospitalized adolescents found a significant difference between response rates for DVPX-QTP combination treatment (87%) and DVPX alone (53%).[34] Finally, in a 6-month, open-label, prospective trial of combination treatment with either risperidone and lithium (RIS + LI) or risperidone and DVPX (RIS + DVPX) in 37 acutely manic or mixed BPD youths, Pavuluri and associates[35] reported similar response rates (defined as ≥50% decline from baseline YMRS) and remission (defined as ≥50% change from baseline YMRS, CGI ≤ 2, and CGAS ≥ 51) for the two groups—80% and 60%, respectively, for RIS + DVPX, and 82% and 65%, respectively for RIS + LI, with large effect sizes of 2.82 and 4.36, respectively.

These studies, taken together, suggest that combination therapy with adjunctive mood stabilizers or antipsychotic agents can improve response rates, particularly in those children with moderate to severe symptomatology. The

TABLE 3. Select Comparison Studies in the Treatment of Juvenile Bipolar Disorder

	Design	Entry criteria/age (mean)	Target serum level; dose; mean serum level achieved	*N* at entry/ retained	Outcome measures	Concurrent medications	Definition of outcome/efficacy results
Kowatch et al. (2000)[14]	6-wk open, prospective, outpatient monotherapy trial of DVPX vs. Li+ vs. CBZ	DSM-IV BPD I/II, mixed or manic;YMRS ≥ 14; age 6–18 (11.4 ± 3.0)	Li+: target, 0.8–1.2 mEq/L; dose, 30 mg/kg/d; achieved, 0.88 ± 0.35 mEq/L DPVX: target, 85–10 μg/mL; dose, 20 mg/kg/d; achieved, 82.8 ± 22.92μg/mL CBZ: target, 7–10 μg/L; dose, 15 mg/kg/d; achieved, 7.11 ± 1.79 μg/L	42	CGI, YMRS Response: CGI ≤ 2 or ↓YMRS ≥ 50%	Antipsychotics	Mean YMRS and CGI response: DVXP, 46%; Li+, 42%; CBZ, 34% Effect size: DVPX, 1.63; Li+, 1.06; CBZ, 1.00
Findling et al. (2005)[32] (extension of Findling et al. 2003)[23]	Multiphase study Phase 2: 76-wk, randomized, double-blind, maintenance trial of DVPX and Li+ (monotherapy)	DSM-IV BPD I/II, hypomanic, manic, mixed, depressed, euthymic; age 5–17 (10.8 ± 3.5);	Li+: target, 0.6–1.2 mEq/L; dose, 30 mg/kg/d; achieved, 94 ± 0.26 mEq/L DVPX: target, 50–100 μg/mL; dose, 20 mg/kg/d; achieved, 81.1 ± 20.5 μg/mL	60 randomized to either DVPX (30) or Li+ (30) after achieving remission on open-label DVPX + Li+ combination treatment	Primary: relapse and premature discontinuation for any reason Secondary: CDRS-R, YMRS, CGI, CGAS Remission: CDRS-R ≤ 40, YMRS ≤ 12.5, CGAS ≥ 51 (all for 4 consecutive weeks)	Stimulants (58.3%)	63.5% of youths exited the study for mood-related reasons (Li+, 60%; DVPX, 66.7%) Time to mood relapse and to discontinuation equivalent for Li+ and DVPX Youths with a younger age of onset more likely to relapse; youths with higher YMRS scores at baseline more likely to discontinue study early No differences between treatment groups on any secondary measure Only 10% completed study

BPD, bipolar disorder; CBZ, carbamazepine; CDRS-R, Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impressions; DVPX, valproate; Li+, lithium; YMRS, Young Mania Rating Scale.

minimum duration of concomitant medication treatment required to sustain long-term symptomatic response is unknown.

Other Mood Stabilizers. CBZ has been shown to be efficacious in youths with BPD in a randomized, 6-week, prospective, open-label comparison trial of DVPX, lithium, and CBZ.[14] As previously noted, CBZ had a response rate of 34% (YMRS $\geq$ 50% change from baseline and CGI $\leq$ 2) and an effect size of 1.0. Furthermore, CBZ's analog, oxcarbazepine, has been shown to be effective in the treatment of BPD in preliminary open-label and retrospective studies in adults[36–39] and in two case reports in youths with BPD.[40,41] Two case reports of using gabapentin in youths with BPD found improved symptoms,[42,43] although placebo-controlled trials of gabapentin in adults with BPD have been negative.[44,45] A retrospective chart review of topiramate in the adjunctive treatment of youths with BPD reported response rates of 73% and 62% (CGI $\leq$ 2) for mania and overall illness, respectively.[46] Furthermore, two case reports suggest topiramate may be an effective adjunctive treatment of mania in youths with BPD.[47,48] Unfortunately, a 4-week, prospective, double-blind, placebo-controlled trial of topiramate in youths with BPD was inconclusive; the study was terminated after a report found topiramate was not superior to placebo in a placebo-controlled trial in acutely manic adults.[49,50] The reduction in mean total YMRS scores, however, was found to be twice as great in the topiramate-treated youths, and topiramate treatment produced a significantly greater improvement in Brief Psychiatric Rating Scale for Children scores.[50] Furthermore, placebo-controlled trials of lamotrigine have been performed for both the acute and maintenance treatment of adults with BPD, with positive results.[51,52] Studies of the use of lamotrigine are sparse. One small, retrospective study of 9 adolescents with refractory mood disorders (6 with BPD) found that 8 of the 9 youths improved as measured by a CGI of "much improved" or "very much improved."[53]

Overall, the data supporting the efficacy of the newer mood stabilizers in the treatment of juvenile BPD is limited. Given the increasing utilization of these mood stabilizers and the lack of rigorous studies evaluating the efficacy of these potentially promising agents in juvenile BPD, randomized, controlled studies are warranted.

Aggression

Disruptive behavioral disorders—a heterogeneous group of psychiatric disorders that often includes conduct disorder (CD), oppositional defiant disorder (ODD), and ADHD—are frequently associated with high rates of comorbid mood and anxiety disorders.[54,55] The use of pharmacologic treatment in disruptive behavioral disorders is often symptom focused, particularly in regard to aggression. Aggression is thought to be either reactive (affect laden, impulsive, and explosive) or proactive (calculated, planned, and controlled), with the former type being responsive to medications, including mood stabilizers.[55,56]

Lithium. Lithium has been shown to be more effective than placebo in the treatment of aggression in three placebo-controlled trials of inpatient youths with CD, aggressive type.[57–59] In a 6-week, inpatient, placebo-controlled trial of 50 children with CD, undersocialized aggressive type, Campbell and associates[58] reported response rates on the Global Clinical Judgments Consensus Scale (GCJCS) (response defined as 1 ["marked improvement"] or 2 ["moderate improvement"]) of 40% in the placebo group, compared to 68% in lithium-treated youths. When a more strict criterion was applied (GCJCS = 1) response rates were 40% for the lithium-treated youths and 4% for the placebo group.[58] In a similar inpatient, double-blind, placebo-controlled study of adolescents with CD, aggressive type, response rates (GCJCS $\leq$ 2 and CGI $\leq$2) were 80% and 70%, respectively, for the lithium-treated youths, compared to 30% and 20%, respectively, for the placebo group.[59] Scores on the Overt Aggression Scale (OAS) also decreased significantly for the lithium-treated group as compared to the placebo group.[59] Finally, in a 4-week, double-blind, placebo-controlled inpatient study of children with CD, aggressive type, lithium was found to be as effective as haloperidol, with both treatment groups being superior to placebo on the CGI and the Aggression, Hyperactivity, and Hostility clusters on the Children's Psychiatric Rating Scale (CPRS).[57] Although not significant, twice as many children were markedly improved on lithium relative to haloperidol on the GCJCS, and there were fewer reported side effects in the lithium-treated youths.[57] Smaller studies also support the use of lithium in reducing aggression.[60–63] However, in a 2-week, double-blind, placebo-controlled trial of lithium in 33 adolescents with CD, Rifkin and associates[64] found lithium to be no more efficacious than placebo. Negative findings have likewise been reported in an open, prospective study by Klein and colleagues.[65] Discrepant results may be accounted for by differences in study design and patient characteristics. For example, Rifkin and associates[64] incorporated a shorter, 1-week baseline period (vs. 2 weeks), a shorter, 2-week treatment (vs. 4 to 6 weeks), and a high percentage of females (58% vs. 7% to 17 %). Much to the same effect, Klein and colleagues[65] did not perform a 1- to 2-week baseline assessment of their outpatients, who likely had lower levels of aggressivity as they did not require hospitalization.

Given the strength of the placebo-controlled studies, it appears that lithium is an effective treatment for the reactive subtype of aggression in youths (see Table 4).

TABLE 4. Select Studies of Mood Stabilizer Treatment in Aggression

	Design	Entry criteria/age (mean)	Target serum level; dose; mean serum level achieved	*N* at entry/ retained	Outcome measures	Concurrent medications	Definition of outcome/efficacy results
Lithium							
Campbell et al. (1984)[57]	2-wk, inpatient, double-blind, controlled trial of Li+ vs. HAL vs. placebo in treatment-resistant youth	DSM-III CD w/ aggressivity; age 5–13 (mean, 8.97)	Li+: target, ≤ 1.8mEq/L; dose, ≤2000 mg/d (mean, 1166 mg/d); achieved, 0.99 mEq/L HAL: dose, 1–6 mg/d (mean, 2.95 mg/d)	61 (21, Li+; 20, HAL; 20, placebo) 93% male	CPRS, CGI, CTQ, PTQ, GCJCS, TORSA	None	Li+ and HAL were equally effective; both better than placebo in reducing target symptoms and the hyperactivity, hostility, and aggression clusters of CPRS; HAL associated with more side effects
Campbell et al. (1995)[58]	6-wk, inpatient, double-blind, placebo-controlled Li+ trial	DSM-III-R undersocialized, aggressive type; age 5–12 (9.4 ± 1.8)	Target, ≤1.8 mEq/L; dose, ≤2100 mg/d (mean, 1248 mg/d); achieved, 1.12 mEq/L	50 (25, Li+; 25, placebo) 92% male	GCJCS, CPRS, CGI, CTQ, PTQ, POMS Response: GCJCS ≤ 2	None	Response rates: Li+, 68%; placebo, 40%* GCJCS response of 1: Li+, 40%; placebo, 4%
Rifkin et al. (1997)[64]	2-wk, inpatient, double-blind, placebo-controlled trial of Li+; ≥3 aggressive acts weekly	DSM-III CD; age 12–17 (15.2 ± 1.5)	Target, 0.6–1.0 mEq/L; achieved (mean), 0.79 mEql/L	33 enrolled (14, male; 19, female) 26 completed (14, Li+; 12, placebo)	OAS, BRS, HAM-D, CTQ Remission: absence of threshold ratings for admission to study		No significant differences on any measure for Li+ vs. placebo Remission: Li+, 21.4%; placebo, 8.3%
Malone et al. (2000)[59]	4-wk, inpatient, double-blind, placebo-controlled Li+ trial; ≥3 aggressive acts weekly and OAS ≥ 18	DSM-III-R CD w/ aggressivity; age 10–17 (mean, 12.5)	Target, 0.8–1.2 mEq/L; dose, ≤2100 mg/d (1425 ± 321 mg/d); achieved, 1.07 ± 0.19 mEq/L	40 (20, Li+; 20, placebo) 83% male	CGI, GCJCS, OAS Response: GCJCS ≤ 2 and (separately) CGI ≤ 2	None	GCJCS response rates: Li+, 80%; placebo, 30%* CGI response rates: Li+, 70%; placebo, 20%* OAS decreased significantly for Li+ vs. placebo*
Valproate							
Donovan et al. (1997)[66]	5-wk, open-label DVPX trial	DSM-III-R CD or ODD; chronic temper outburst and mood lability; age 13–20	Dose, 1000 mg/d; achieved (mean) 75μg/mL	10 subjects	MOAS, GBI, GAF		Significant reductions in the number of outburst and in mood lability*

Donovan et al. (2000)[68]	Double-blind, placebo-controlled, cross-over DVPX study, w/ each of 2 phases lasting 6 wk	DSM-IV CD or ODD; explosive temper or mood lability; age 10–18 (13.8 ± 2.4)	Dose, 750–1500 mg/d; achieved, 82.2 ± 19.1 μg/mL	20 enrolled 17 completed first phase 15 completed both phases 80% male	MOAS, SCL-90 Response: ≥70% decrease in MOAS and anger-hostility subscale of SCL-90	Stimulants (number not reported)	Phase 1 response: DVPX, 8/10; placebo, 0/10 Phase 2 response: DVPX, 6/7 (86%); placebo, 2/8 (25%)
Steiner et al. (2003)[69]	7-wk, double-blind, randomized, controlled trial of high- and low-dose DVPX in institutionalized adolescents	DSM-IV CD w/ at least one offense against persons; age 14–18 (15.9 ± 1.1)	High-dose group: target, 50–120 μg/mL; dose, 500–1500 mg/d (mean, 1000 mg/d); achieved, 71.2 ± 22.8 μg/mL Low-dose group: dose, ≤250 mg/d (mean, 125 mg/d; achieved, 13.8 ± 5.12 μg/mL	58 (34, high dose; 24, low dose) 100% male	CGI, WAI, YSR Response: CGI ≤ 2		Response rates: high dose, 58%; low dose, 8%* For responders, significant improvement in self-reported impulse control*
Carbamazepine							
Cueva et al. (1996)[73]	6-wk, double-blind, placebo-controlled study of CBZ; Hx treatment resistance; ≥3 aggressive acts weekly	DSM-II-R CD, aggressive type; age 5–12 (mean, 8.97)	Dose, 400–800 (not to exceed 1000) mg/d (mean, 683mg/d); achieved, 6.81 μg/mL	24 enrolled 22 completed 91% male	CPRS, CGI, CTQ, PTQ, OAS, GCJCS	None	On all measures, no significant differences between CBZ and placebo

BRS, Behavioral Rating Scale; BPRS, Brief Psychiatric Rating Scale; CBZ, carbamazepine; CD, conduct disorder; CPRS, Children's Psychiatric Rating Scale; CGI, Clinical Global Impressions; CTQ, Conner's Teacher Questionnaire; DVPX, valproate; GAF, Global Assessment of Function; GBI, General Behavioral Inventory; GCJCS, Global Clinical Judgments Consensus Scale; HAL, haloperidol; HAM-D, Hamilton Rating Scale for Depression; Li+, lithium; MOAS, Modified Overt Aggression Scale; OAS, Overt Aggression Scale; ODD, oppositional defiant disorder; POMS, Profile of Mood States; PTQ, Conner's Parent Teacher Questionnaire; TORSA, Timed Objective Rating Scale for Aggression; WAI, Weinberger Adjustment Inventory; YST, Achenbach Youth Self-Report.

*Statistically significant at $p < 0.05$.

Valproate. DVPX has been founded to be effective for aggression in open-label,[66] naturalistic,[67] and controlled studies.[68,69] For example, in a recent 5-week, open-label trial of DVPX in 10 adolescents with ODD or CD characterized by chronic temper outbursts or mood swings, there was clear improvement in the number of outbursts and mood lability.[66] In a 6-week, double-blind, placebo-controlled crossover trial in 20 adolescents with CD or ODD characterized by explosive temper or mood lability, 80% responded to DVPX (≥70% reduction from baseline in the Modified Overt Aggression Scale and the anger-hostility subscale of the Symptom Checklist–90) during the first phase (vs. no responders in the placebo group), and 86% responded during the second phase (vs. 25% in the placebo group).[68] Furthermore, a 7-week, double-blind, randomized, controlled trial of high- and low-dose DVPX in 58 institutionalized adolescents with CD found a significant difference in response rates—58% versus 8%, respectively.[69] Youths in this study reported significant improvements in impulse control. In a related study—a post hoc analysis of a prior study[34]— DelBello and associates[70]looked at mean scores of standard assessment items for aggression, irritability, and impulsivity in 15 adolescents with mania who were treated with monotherapy DVPX for 6 weeks. There were significant reductions in the YMRS aggression and irritability items, CDRS irritability item, and Positive and Negative Syndrome Scale impulsivity item.[70]

Taken together, these studies suggest that DVPX is effective in reducing impulsivity, aggression, and affective instability in youths with disruptive behavioral disorders.

Carbamazepine. A large review of CBZ in 28 clinical trials in the 1970s—involving more than 800 non-epileptic children—suggested that symptoms of emotional lability, impulsivity, and aggression may respond to CBZ.[71] In a more recent, open study of CBZ in 10 children with CD characterized by severe aggression and explosivity, there were significant reductions of target symptoms on several measures.[72] However, in a 6-week, double-blind, placebo-controlled study in 24 children with treatment-resistant CD, aggressive type, CBZ was no better than placebo.[73]

Pervasive Developmental Disorders

Pervasive developmental disorders (PDD) include a spectrum of disorders such as autism and Asperger's syndrome, and are characterized by impairment in the core areas of social interaction, communication skills, and restricted and stereotyped patterns of behavior, activities, and interests.[74] The rate of comorbidity in PDD is high, and symptoms of affective instability, impulsivity, and aggression are common.[75] Preliminary studies suggest that mood stabilizers may be effective in the treatment of both core and associated symptoms of PDD. For example, in an open-label, retrospective study of DVPX involving 10 youths and 4 adults with autism spectrum disorder, 71% responded to DVPX treatment (CGI ≤ 2), and improvements were noted in both core autistic symptoms and in associated symptoms such as affective instability, impulsivity, and aggression.[75] In another study, DVPX was found to improve language acquisition and socialization in young epileptic children with autism spectrum disorders.[76] Furthermore, case reports have suggested that lithium may be helpful for some autistic patients who have symptoms of mania and a positive family history of BPD.[77,78] In a recent retrospective study of topiramate in 15 children and adolescents with PDD, authors noted a response (CGI ≤ 2) rate of 60%.[79] Furthermore, specific target symptoms on the Conner's Parent Scale, including conduct, inattention, and hyperactivity, also improved.[79] In an open-label study of children with intractable epilepsy and PDD, lamotrigine improved autistic symptoms in 8 of 13 youths.[80] However, in a double-blind, placebo-controlled study of 28 children with PDD that examined the effects of lamotrigine compared to placebo on core and associated features of autism, the results were negative.[81]

In summary, preliminary data suggest that mood stabilizers, particularly DVPX, are effective for both core and associated symptoms of PDD; however, further controlled studies are needed.

Depression

Lithium augmentation of an antidepressant was found to improve mood symptoms in a case report of 2 adolescents with major depressive disorder (MDD).[82] In a retrospective study of 14 adolescents with MDD, lithium augmentation of a tricyclic antidepressant led to significant improvement in mood and psychosocial factors.[83] In a 3-week open trial of 24 adolescents who did not respond to 6 weeks of imipramine treatment, lithium augmentation was found to significantly reduce HAM-D scores.[84] However, in a 6-week, double-blind, placebo-controlled outpatient study of lithium in the treatment of prepubertal depressed children with a family history of predictors for BPD, there were no significant differences in clinical measures between placebo and lithium-treated youths.[85] The youths in this study were notable for mood severity, chronicity, and high rates of comorbidity, which are factors associated with treatment resistance. Lithium nonresponse in prepubertal-onset juvenile BPD has also been described.[12] Interestingly, tricyclic antidepressants have been found ineffective in the treatment of youths with MDD.[86,87] Clinically, these findings suggest that mood symptoms in youths, particularly in

prepubertal youths, are difficult to treat, which indicates the need for further investigations of alternative agents and of the safety and efficacy of combination treatment in youths with MDD.

Safety and Tolerability Data

The recommended target dose of lithium in youths is 30 mg/kg/d, with desired serum levels of 0.6–1.2 mEq/L.[88] The studies cited in this review—with dosages in the ranges of 10–30 mg/kg/d and levels of 0.6–1.5 mEq/L—accord with those guidelines. The most common side effects of lithium are gastrointestinal symptoms (including nausea, vomiting, and diarrhea), polyuria, polydipsia, enuresis, and fatigue, with more severe side effects including hypothyroidism and cardiac conduction abnormalities.[88] Indeed, the most common side effects reported for the acute lithium monotherapy studies in this review were dizziness, gastrointestinal symptoms, polydipsia, polyuria, tremor, and weight gain (or an increase in appetite) (see Table 5). Most of the studies reported that side effects were mild to moderate, and that the dropout rate was low. No serious adverse events were reported in the monotherapy lithium trials. In a study of combination lithium-DVPX treatment, however, 15 of 90 subjects, or 16.7%, withdrew because of medication intolerance.[23] Twelve of those 15 likely withdrew from lithium-associated side effects (5 for ataxia and neurologic effects, 3 for persistent thyrotropin elevation, and 1 each for proteinuria, enuresis, emesis, and dysphoria) and 2 from DVPX-associated side effects (1 for increased liver enzymes and 1 for worsening manic symptoms).[23] When lithium was used in combination with risperidone, 2 of 17 subjects, or 11.8%, withdrew from the study for enuresis and fatigue.[35] In another study of lithium with adjunctive antipsychotic treatment, the authors reported that 8 of 35 youths, or 22.9%, experienced moderate impairment, although only 1 of these 8 withdrew from the study (for nausea and vomiting).[22]

Late-appearing side effects of lithium treatment in youths may include hypothyroidism and kidney effects such as glomerulosclerosis.[88] Unfortunately, studies evaluating the effects of chronic lithium administration in youths have not been performed. In a 76-week maintenance trial of lithium, however, only 2 of 30 youths with BPD discontinued treatment secondary to side effects (alopecia and enuresis).[32] The longer-term safety and tolerability of lithium treatment in youths has been also suggested by other studies.[62,89]

For DVPX, the recommended target dose is 10–20 mg/kg/d, with therapeutic serum levels of >50 ug/mL.[88] The target doses and levels used in the reported studies were 15–20 mg/kg/d and 45–130 ug/mL. The most common side effects for DVPX include gastrointestinal symptoms, weight gain, drowsiness, rash, muscle weakness, and hair loss, with more worrisome, albeit rare, side effects including thrombocytopenia, hepatic toxicity, and polycystic ovaries.[88] In the acute monotherapy studies of DVPX, the most common side effects were gastrointestinal symptoms, headaches, sedation, dizziness, and increased appetite or weight gain. In one study, 12 of 40 youths, or 30%, had abnormal laboratory values that were deemed not clinically significant.[28] In another study, however, Deltito and associates[27] reported that 3 of 36 youths, or 8.3%, discontinued DVPX for gastrointestinal distress (2 of the 3) and alopecia (1), and that another individual was noted to have elevated liver enzymes. In combination treatment of DVPX and risperidone, one study noted that 2 of the 20 youths studied, or 10%, had prolactin elevation with galactorrhea and breast swelling, and that another 10% had a transient elevation in alanine transferase.[35] In a 76-week maintenance treatment study of DVPX, 2 of 30 youths, or 6.7%, developed alopecia, and 1 developed thrombocytopenia.[32] In a 6-month DVPX study, 6 of 34, or 17.6%, were noted to have transient, abnormally elevated alanine transferase levels that normalized after 2 months of treatment.[29]

For CBZ, the target dose is 10–20 mg/kg/d, with serum levels of 4–14 ug/mL.[88] The reported target dose and serum levels in one study were 15 mg/kg/d and 7–10 ug/mL, respectively.[14] Common side effects include transient leukopenia, rash, dizziness, diplopia, and headaches, with severe side effects including SIADH, neutropenia, and agranulocytosis.[88] In one study, gastrointestinal distress, dizziness, and rash were the most common side effects.[14] In another, transient marked (2 of 13, or 15.4%) and moderate (4 of 13, or 30.8%) leukopenia were reported.[73]

Gabapentin, lamotrigine, and topiramate have been approved for use as adjunctive agents in partial seizures in children above 12 years of age. with recommended target doses of 900–1800 mg/d, 400 mg/d, and 150 mg/d, respectively.[88] Side effects of gabapentin include somnolence, dizziness, ataxia, fatigue, and nystagmus.[88] Although safety and tolerability data are not available for youths with psychiatric disorders, two placebo-controlled trials of gabapentin in adults reported the medication was well tolerated, with the most commonly reported side effects being somnolence and dizziness, diarrhea, headache, ataxia, and diplopia.[44,45] In one of these studies, 7 of 58 adults, or 12.1%, experienced an adverse event, which was either a manic reaction or psychosis.[44] Lamotrigine's side effects include dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea and vomiting, and rash, which can progress to Stevens Johnson syndrome.[88] In a retrospective study of lamotrigine use in 9 adolescents with treatment-refractory mood disorders, 1 youth developed a nonserious rash.[53] In one of the largest double-blind, placebo-controlled studies in adults with BPD, lamotrigine was associated

TABLE 5. Select Studies Reporting Safety and Tolerability Data

	Polydipsia	Polyuria	Nausea	Emesis	Stomach pain	Diarrhea	Dizziness	↑Appetite or weight	Headache	Tremor	Enuresis	Somnolence or sedation	Other	Comments
Lithium monotherapy														
Campbell et al.(1984)[57]														
Lithium ($n = 21$)			√++[a]	√++	√+++		√+		√++	√++		√+++	↓appetite; pallor; ↓verbal production; tearful; subdued; glazed look; ↓motor activity; fidgety; ataxia; dysarthria (5%)	
Haloperidol ($n = 20$)										√++		√+++	Drooling, 30%; acute dystonic reaction, 50%	Side effects seemed to interfere with child's daily functioning more than Li+ or placebo
Strober et al. (1988)[12] ($n = 50$)														2 discontinued Li+ (1 for rash, 1 for tremor); 70% in ADHD group, and 76.7% in non-ADHD group, had at least one side effect
Campbell et al. (1995)[58] ($n = 25$)	√+	√++	√++	√++	√+++	√+		√++	√++	√++	√+		Salivation; double vision; ↓appetite; unsteady gait; ataxia, 4%; blurry vision, 8%	Placebo group also had side effects, although no comparison between the 2 groups was done
Geller et al. (1998)[85] (Li+, $n = 13$; placebo, $n = 12$)	√+++	√+++	√	√			√							Polyuria and polydipsia were significantly different between groups
Malone et al. (2000)[59] (Li+, $n = 20$; placebo, $n = 25$)	√+++	√+++	√+++	√++	√+++	√++	√++	√++	√+++	√++	√+		↓Weight and rash, 15%; other (constipation, decreased appetite, sore throat, muscle pain, painful urination, twitching depression, weakness), 35%	Only emesis and polyuria were significantly different between Li+ and placebo
Kafantaris et al. (2003)[9] ($n = 100$)	√+++	√++	√++	√++	√++	√++		√++	√++	√++			Anorexia	3 discontinued (2 for GI symptoms, 1 for diplopia); side effects elicited from >10% sample at 4 wk

Valproate monotherapy (BPD)													
Wagner et al. (2002)[28] (n = 40)		√++	√++		√++			√++			√++		68% w/ mild to moderate side effects; 2 adverse events (rash); 3 serious adverse events not attributable to DVPX (behavioral abnormality, suicidality, manic-depressive reaction)
Pavuluri et al. (2005)[29] (n = 35)		√++		√++			√+++		√++		√+++	41.2%, cognitive dulling; 17.6%, agitation	6 of 35 had transient ↑transaminase that normalized after 2 months of treatment
Combination therapy													
Kafantaris et al. (2001)[22] (n = 35)													71.4%, minimal functional impairment; 22.9%, moderate impairment; 1 discontinued (GI symptoms)
DelBello et al. (2002)[34]													
DVPX + placebo (n = 15)		√+++	√+++	√+++		√++		√+++			√+++	Joint pain, 13%; dry mouth, 13%	
DVPX + QTP (n = 15)		√++	√++	√+++		√+++		√+++			√+++	Joint pain, 13%; dry mouth, 33%	Sedation more common in DVPX + QTP group (80%) (= only side effect significantly different between groups)
Findling et al. (2003)[23] DVPX + Li+ (n = 90)	√+++	√+++	√+++	√+++	√++	√+	√++	√+++	√+++	√+++	√+++	↓appetite, 17%; upper respiratory congestion, 16%; fever, 14%; body ache, 11%	16.7% w/drew (medication intolerance) 80% of these w/drawals thought to be secondary to Li+: ataxia/neurologic side effects, 5; persistent ↑TSH, 3; proteinuria, 1; enuresis, 1; emesis, 1; dysphoria, 1 13.3% of w/drawals thought to be secondary to DVPX: ↑transaminase, 1; ↑mania, 1

(Continued on next page)

TABLE 5. Select Studies Reporting Safety and Tolerability Data *(Continued)*

	Polydipsia	Polyuria	Nausea	Emesis	Stomach pain	Diarrhea	Dizziness	↑Appetite or weight	Headache	Tremor	Enuresis	Somnolence or sedation	Other	Comments
Pavuluri et al. (2004)[35]														
RIS + Li+ ($n = 17$)		√++	√++		√++			√+++		√++		√++	Cognitive dulling, 18%; akathisia, 6%; buccolingual movements, 6%	2 discontinued (1 for enuresis, 1 for fatigue)
RIS + DVPX ($n = 20$)			√++		√++			√+++		√++		√++	Cognitive dulling, 15%; akathisia, 10%	No one discontinued; 2 experienced ↑prolactin w/ galactorrhea and breast swelling; 2 experienced transient ↑alanine transferase
Comparison studies														
Kowatch et al. (2000)[14]														
Lithium ($n = 14$)		√+	√++			√+		√++					GI symptoms	
CBZ ($n = 13$)			√+++				√+					√++	Rash, 8%	
DVPX (n = 15)			√++									√++		
Findling et al. (2005)[32]														75% experienced side effects, w/ 5 of 60 (8.3%) discontinuing as a result
Lithium ($n = 30$)	√++		√++	√+++	√++	√++			√++	√++	√+++		↓appetite, 10%; upper respiratory congestion, 6.7%; fever, 13.3%; sore throat, 3.3%	Significant ↑thirst, enuresis in Li+ group vs. DVPX group; 2 discontinued (1 for alopecia, 1 for enuresis)
DVPX ($n = 30$)			√+	√++	√++	√+			√++	√++	√+		Decreased appetite, 10%; upper respiratory congestion, 10%; fever, 3.3%; sore throat, 10%	3 discontinued (2 experienced alopecia; 1, ↑TSH; 1, thrombocytopenia)

ADHD, attention-deficit/hyperactivity disorder; CBZ, carbamazepine; DVPX, valproate; GI, gastrointestinal; Li+, lithium; QTP, quetiapine; RIS, risperidone; TSH, thyrotropin.

[a]Side-effect ratings: √ = reported side effect only; √+ = <10% reported side effect; √++ = 10–29% reported side effect ; √+++ = ≥30% reported side effect.

most commonly with headache, infection, influenza, nausea, abnormal dreams, dizziness, and rash.[51] Treatment-related, but nonserious, rashes developed in 8% of the adults.[51] Topiramate is associated with weight loss, word-finding difficulties, poor concentration, and fatigue.[88] The most common side effects reported in one retrospective[46] and one double-blind, placebo-controlled study[50] were cognitive disturbance, gastrointestinal distress, sedation, decreased appetite, and paresthesia.

Overall, side effects from lithium and anticonvulsants are common but typically mild to moderate, though dangerous or even fatal side effects can also occur. Several important factors—such as age, gender, compliance, illness severity, side-effect profile, and comorbidity—need to be taken into account before these agents are prescribed. For example, given the association of DVPX with polycystic ovary disease and with fetal anomalies when used during pregnancy, gender is relevant when considering treatment with DVPX. Furthermore, the common side effects of weight gain and acne will reduce compliance rates among teenagers. Overall, mood stabilizers should be used judiciously, with careful consideration of the agents' efficacy and side-effect profiles versus the long-term sequelae of undertreatment, such as severe mood instability, aggression, substance abuse, and other high-risk behaviors, which are often seen in youths with severe psychopathology. In summary, further investigation into the efficacy and safety of mood stabilizers is needed to assist in clinical decision making since current use has outpaced research. Furthermore, head-to-head comparisons of both the efficacy and safety of lithium and anticonvulsants versus atypical antipsychotic agents are urgently needed since mood stabilizers may have a better side-effect profile than atypical antipsychotics, which are increasingly being used as mood-stabilizing and antiaggressive agents.[4]

CONCLUSION

Mood stabilizers, particularly lithium and DVPX, have been reported to reduce affective instability, aggression, and impulsivity across psychiatric disorders in youths. Evidence supporting the use of both lithium and DVPX in reactive aggression and in the acute and maintenance treatment of juvenile BPD has grown. Combination pharmacotherapy with a mood stabilizer and an antipsychotic medication appears to more effective than monotherapy in juvenile BPD. The data are still limited for the use of newer mood stabilizers and for the use of mood stabilizers in youths with other psychiatric illnesses. Overall, side effects from both lithium and DVPX are common but typically mild to moderate. Data are accumulating in regard to the longer-term safety of lithium and DVPX in the juvenile psychiatric population. However, the short- and long-term safety profiles for newer mood-stabilizing agents are limited. Further double-blind, placebo-controlled trials of mood stabilizers are needed—particularly with regard to the newer agents. Reports suggest that they may be effective in the treatment of BPD, aggression, PDD, and treatment-refractory depression, and that they may have better side-effect profiles than the older agents.

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