Current PSYCHIATRY

Are anticonvulsants safe for pediatric bipolar disorder?

Using antiepileptic agents as mood stabilizers requires caution

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Are anticonvulsants safe and effective mood stabilizers for children and adolescents with bipolar disorder? The answer is unclear because most bipolar disorder treatment trials have included adults only, and clinicians are desperate for data.[1]

To help you care for young patients, we report what is known about the potential benefits and risks of using mood stabilizers and anticonvulsants in bipolar youth. We base our dosing, target serum level, and monitoring recommendations

Table 1

FDA-approval status of medications used to treat bipolar disorder

Medication	Indications for adults	Indications for children
Carbamazepine	Acute manic episode and acute mixed episode	Not approved
Lamotrigine	Maintenance therapy	Not approved
Lithium	Acute manic episode and maintenance therapy	Age ≥ 12 years
Oxcarbazepine	Not approved	Not approved
Topiramate	Not approved	Not approved
Valproate	Acute manic episode	Not approved

Source: Reference 3

on clinical experience and the limited published evidence.

AGENTS OF CHOICE?

Bipolar disorder's "atypical" presentation in children—often more irritability and explosiveness than euphoria—can complicate diagnosis. Bipolar children and adolescents often have comorbid attention-deficit/hyperactivity disorder (ADHD), other disruptive behavior disorders, or anxiety disorders. Thus, comorbidities and presenting symptoms often dictate medication choice.

An expert consensus guideline acknowledges that more evidence on pediatric bipolar disorder is needed. In the meantime, the guideline suggests trying valproate or lithium first to treat nonpsychotic mania in pediatric bipolar patients.[1] It also recommends three atypical antipsychotics—olanzapine, quetiapine, and risperidone—as potential first-line treatments. Valproate and lithium may be preferred because of atypicals' risk of weight gain and metabolic syndrome.

Trying other anticonvulsants may be justified for bipolar youths who are not functioning well with first-line agents. Lamotrigine, for example, has antidepressant and antimanic effects.[2] When you try anticonvulsants that lack double-blind, placebo-controlled trials, we recommend that you:

- obtain consent from the parents and child
- monitor carefully for side effects.

Valproate or lithium are first-line options for nonpsychotic mania in pediatric bipolar patients

LITHIUM: STRONGEST EVIDENCE

Lithium is one of the most well-studied medications for pediatric bipolar disorder and the only mood stabilizer FDA-approved for children and adolescents (*Table 1*).[3] Although approved for ages 12 and older, lithium has been used in younger children in practice and in clinical trials.

Efficacy. In an open-label study of 100 adolescents with type I bipolar disorder,[4] 63% met response criteria after 4 weeks of lithium and 26% showed manic symptom remission. Symptoms worsened in both groups, however, when 40 responders were randomly assigned to continue or discontinue lithium for 2 weeks.[5] The authors speculated that these conflicting results might indicate that mood stabilization requires longer treatment. Contrary to earlier reports,[6] manic adolescents with comorbid ADHD did not show poor response to lithium.

Table 2

Guide to dosing lithium for prepubertal school-aged children*

Child's weight (kg)	Doses (mg) 8 AM	12 PM	6 PM	Total daily
<25	150	150	300	600
25 to 40	300	300	300	900
40 to 50	300	300	600	1,200
50 to 60	600	300	600	1,500

* Maintain specified dose at least 5 days, drawing serum levels 12 hrs after the last lithium dose until two consecutive levels appear in the therapeutic range (0.6 to 1.2 mEq/L). Dose may then be adjusted based on serum level, side effects, or clinical response. Do not exceed 1.4 mEq/L.

Source: Reference 8

In the only double-blind, placebo-controlled trial of lithium in adolescents with bipolar disorder, some subjects had secondary substance dependency disorders.[7] For 6 weeks, 25 outpatient adolescents received lithium (13 patients) or placebo (12 patients). Lithium was effective in treating bipolar and substance dependency symptoms, with significantly improved clinical global assessment scores and decreased positive urine assays for drugs. Little difference was seen in mood item scores on the Schedule for Affective Disorders and Schizophrenia, child version (K-SADS-1986), whether patients were taking lithium or placebo.

In 3 open-label trials, 53% to 80% of pediatric bipolar patients responded to valproate therapy

Pediatric dosing. For bipolar patients ages 6 to 12, use the child's weight to determine lithium dosage (*Table 2*).[8] Maintain serum levels between 0.8 and 1.2 mEq/L,[9] and check them frequently when starting therapy.[10] After mood stabilization, check levels every 1 to 3 months or when you suspect noncompliance. Obtain renal and thyroid function values at baseline and every 4 to 6 months.

Safety. Common side effects reported in adolescents include weight gain (55%), polydipsia (33%), polyuria (25%), headache (23%), tremor (20%), and GI complaints (up to 18%).[4] Neurologic side effects are associated with higher serum lithium levels (0.91 to 1.36 mEq/L)[10] and occur more often in younger than in older children.[11] The cardiac defect Ebstein's anomaly occurs in approximately 0.05 to 0.1% of children exposed to lithium in utero (*Box, page 37*).[12-16]

VALPROATE: OPEN-LABEL TRIALS ONLY

Efficacy. No double-blind, placebo-controlled study has shown valproate to be effective in treating bipolar disorder in children and adolescents. When used as monotherapy in open-label studies, valproate has produced response rates of:

- 53% in a 6-week, randomized, open-label trial in which 42 outpatients (mean age 11.4 years) with bipolar disorder type I or II received lithium, divalproex sodium, or carbamazepine[9]
- 61% in an open-label study of 40 patients ages 7 to 19 with a manic, hypomanic, or mixed episode who received divalproex for 2 to 8 weeks[17]
- 80% in an 8-week open-label trial of 40

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patients ages 6 to 17 with bipolar disorder type I (77.5%) or type II (22.5%) and a Young Mania Rating Scale (YMRS) score ≥ 14.[18]

In a prospective trial, 90 patients ages 5 to 17 with bipolar disorder type I or II were treated with lithium plus divalproex sodium. After up to 20 weeks, 47% met criteria for depressive and manic symptom remission.[19] A chart review has showed valproate's efficacy in treating aggression and irritability in adolescent mania.[20]

Safety: Black-box warnings. Valproate therapy carries risks of hepatic failure, pancreatitis, and birth defects. Monitor blood counts and hepatic enzymes throughout therapy (*Table 3, page 38*).[3] Rare yet potentially fatal hepatic toxicity appears to occur most often in children age <2 who are treated with anticonvulsant combinations.[21] Other studies suggest:

- an association with congenital malformations, including spina bifida and pulmonary atresia, in children exposed to valproate in utero[6]
- a link between valproate and hyperammonemic encephalopathy, especially in patients with urea cycle disorders[22]
- potential for benign thrombocytopenia[23]
- increased incidence of polycystic ovary syndrome—ovarian cysts, hyperandrogenism, chronic anovulation—in peripubertal mentally retarded women treated with valproate for seizure disorders.[24]

Because of these risks, use caution when prescribing valproate to bipolar adolescent girls. Monitor menstrual cycle regularity, and collaborate with a gynecologist to watch for potentially dangerous effects.

Body weight. Valproate has been associated with weight gain. In a study of 372 bipolar adults, 21% reported a 5% weight-gain during 52 weeks of maintenance therapy, compared with 13% of patients on lithium and 7% on placebo.[25] Short-term studies of adjunctive valproate in pediatric bipolar patients raise similar concerns.[26] Thus,

Box

Birth-defect risks to consider when prescribing mood stabilizers

Consider teratogenicity when choosing mood stabilizers for bipolar adolescent girls who may be sexually active. Lithium, valproate, and carbamazepine are labeled pregnancy category D because of their potential to cause birth defects.

Lithium treatment has been associated with increased risk of cardiac defects, specifically Ebstein's anomaly (malformation of the tricuspid valve). Its incidence in children of women who used lithium during pregnancy is estimated to be 1:1,000 (0.10%) to 2:1,000 (0.05%)—20 to 40 times the rate in the general population.[12]

Valproate. Results from the North American Antiepileptic Drug (AED) Pregnancy Registry showed a 10.7% rate of major congenital malformations (MCM)—including neural tube defects (spina bifida) and cardiac defects (pulmonary atresia)—in children of women who used valproate during pregnancy. The rate of births with MCMs in the general population is 2.9%.[13]

Carbamazepine. Data from the Australian Pregnancy Registry showed no significant increase in malformation rates in infants of carbamazepine users compared with those of women receiving no antiepileptics.[14] Other studies, however, have linked carbamazepine with an increased risk of craniofacial defects (11%), neural tube defects (0.5 to 1%), and cardiac malformations.[12]

Lamotrigine. The teratogenic effects of the newer anticonvulsants are unclear. An 11-year study of lamotrigine[15] found MCM risk after first-trimester exposure to lamotrigine to be similar to the general population's MCM risk.

Combination therapy. Teratogenic risk appears to increase when multiple antiepileptic drugs are used (9.9% risk in polytherapy vs 6.2% in monotherapy).[16]

Table 3

Mood stabilizers' side effects and recommended monitoring

Medication	Major side effects	Monitoring
Carbamazepine	Allergic skin rash, drowsiness, **blood dyscrasias,** diplopia	CBC with reticulocytes, iron, LFTs, urinalysis, BUN, TFTs, sodium, serum carbamazepine levels
Lamotrigine	**Stevens-Johnson syndrome,** headache, dizziness, ataxia, somnolence, nausea, diplopia, blurred vision, rhinitis	No serum monitoring recommended
Lithium	Polyuria, polydipsia, nausea, diarrhea, tremor, enuresis, fatigue, ataxia, leukocytosis, malaise, cardiac arrhythmias, weight gain	BUN/creatinine, creatinine clearance, TFTs, calcium/phosphorus, ECG, serum lithium levels every 1 to 3 months once stabilized
Oxcarbazepine	Dizziness, somnolence/fatigue, ataxia/gait disturbance, vertigo, headache, tremor, rash, hyponatremia, hypersensitivity reaction, GI symptoms, diplopia	Sodium levels (particularly in first 3 months)
Topiramate	Hyperchloremic metabolic acidosis, oligohydrosis and hyperthermia, acute myopia, somnolence/fatigue, nausea, anorexia/weight loss, paresthesia, tremor, difficulty concentrating	BUN/creatinine, sodium bicarbonate
Valproate	Irritability/restlessness, ataxia, headache, weight gain, hyperammonemic encephalopathy, alopecia, GI upset, **pancreatitis,** sedation, thrombocytopenia, **liver failure,** polycystic ovaries/hyperandrogenism, **teratogenic effects,** rash	Ammonia, LFTs, bilirubin, CBC with platelets, serum valproate levels

BUN: blood urea nitrogen; CBC: complete blood count; ECG: electrocardiography; LFT: liver function tests; TFTs: thyroid function tests
Note: Bolded items included in black-box warnings
Source: Reference 3

monitor for weight gain and serum lipid changes in youths starting valproate therapy.

CARBAMAZEPINE: DRUG INTERACTION RISK

Carbamazepine is used less often than lithium or divalproex for bipolar disorder. It tends to be used adjunctively when lithium alone is ineffective.

Efficacy. In an open-label study,[9] 42 patients ages 8 to 18 with bipolar disorder type I or II were randomly assigned to lithium, divalproex sodium, or carbamazepine monotherapy for 6 weeks. Response rates—measured as a ≥ 50% change from baseline in YMRS scores—were 53% with divalproex, 38% with lithium, and 38% with carbamazepine.

A retrospective review of 44 hospitalized bipolar patients ages 5 to 12 treated for at least 7 days with lithium, valproate, or carbamazepine reported higher (ie, worse) Clinical Global Impression of Improvement scores with carbamazepine.[27] Small sample sizes, particularly in the carbamazepine group, limited this naturalistic study.

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Safety: Black-box warnings. Carbamazepine's hematologic "black box" warns of increased risk of aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Risks associated with carbamazepine have been estimated at:

- aplastic anemia: 5.1/million patient years
- agranulocytosis: 1.4/million patient years.[28]

Leukopenia is relatively more common and occurs in approximately 20% of children receiving carbamazepine.[29] Consider stopping carbamazepine when the white cell count falls below 3,000/mm^3 (or the neutrophil count drops to <1,000/mm^3).[29] Advise children and parents to watch for leukopenia's signs and symptoms, including fever, infections, sore throat, and mouth ulcers.[3]

Body weight. Carbamazepine is not associated with significant weight gain, which could be clinically important for some patients.

Drug interactions. Carbamazepine activates the cytochrome P-450 liver enzyme system, increasing the metabolism of many medications and decreasing their blood levels. Consider monitoring serum levels when using carbamazepine with valproate, imipramine, corticosteroids, warfarin, oral contraceptives, and some antibiotics. Because carbamazepine induces its own metabolism, you might need to increase its dosage if its effects appear to be waning.[3]

Carbamazepine and tricyclic antidepressants may show cross-sensitivity because of structural similarity. Do not use monoamine oxidase inhibitors with carbamazepine; discontinue them at least 14 days before starting carbamazepine.[3]

OXCARBAZEPINE: FEWER INTERACTIONS

Oxcarbazepine has similar efficacy to carbamazepine but less side effect risk and does not require plasma level monitoring. A weaker inducer of CYP-450, it causes fewer clinically important drug-drug interactions and may be useful for patients who respond to carbamazepine but cannot tolerate its side effects.[30]

Efficacy. Case studies[31,32] have been encouraging, but no published, double-blind, placebo-controlled studies support using oxcarbazepine in bipolar children and adolescents.

Safety. Oxcarbazepine appears to be generally well-tolerated but can cause potentially serious reactions—including hyponatremia.[33] Somnolence, emesis, and ataxia are the most common side effects in pediatric patients.[3]

With oxcarbazepine, monitor serum sodium carefully if levels fall to 125 to 130 mEq/L

Hyponatremia—plasma sodium ≤ 125 mEq/L—occurs in 2.5% of adults taking oxcarbazepine[3] and has been reported in a similar percentage of children.[34] This potentially severe reaction—characterized by nausea, lethargy, malaise, headache, confusion, decreased seizure threshold, or simply decreased serum sodium[35]—is usually noted within the first 12 weeks of therapy. The risk increases with concomitant use of other sodium-altering drugs, such as antidepressants or antipsychotics.[36]

Evaluate serum sodium when starting oxcarbazepine, periodically in the first 3 months, and if symptoms occur.[34,36] For sodium levels of 125 to 130 mEq/L, obtain repeat measurements to confirm that hyponatremia is not worsening. Intervention is often required when levels fall below 125 mEq/L.[36]

Other serious adverse reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions; 25% to 30% of patients with hypersensitivity to carbamazepine also will react to oxcarbazepine.[33]

Contraceptive concerns. Oxcarbazepine may reduce contraceptive efficacy by altering estrogen and progesterone plasma concentrations.[37] Consider other birth control methods for sexually-active bipolar adolescent girls.

Table 4

Using anticonvulsants in pediatric bipolar disorder patients

Drug	Recommended dosage	Target serum level
Carbamazepine	Age 6 to 12: 20 to 30 mg/kg/d Age >12: 400 to 1,200 mg/d	≥ 7.0 µg/L
Lamotrigine*	Unknown	Unknown
Oxcarbazepine	11 to 16 mg/kg/d (as adjunct)	Unknown
Topiramate*	Unknown	Unknown
Valproate	15 to 20 mg/kg/d	45 to 125 µg/mL (trough) 85 to 110 µg/mL (target)

* No published studies found for efficacious dosage and plasma levels in pediatric bipolar disorder. Dosage supported by case reports only; no studies found examining efficacious plasma levels.

Source: References 3,9, and 17.

LAMOTRIGINE

Neurologists often use lamotrigine for children with atypical seizure disorders, but no controlled data exist on the drug's efficacy and safety in youths with bipolar disorder.

Efficacy. In a prospective, open-label study,[38] 13 adolescents with type I bipolar disorder received lamotrigine, 200 to 400 mg/d. After 12 weeks (mean dosage 241 mg/d), their symptoms had improved as shown by these mean scores:

- Montgomery-Asberg Depression Rating Scale: from 21 at baseline to 4 at endpoint
- Clinical Global Impressions–Severity of Illness scale: from 4 to 1
- Children's Depression Rating Scale (CDRS-R): from 74 to 40
- YMRS: from 20 to 6.

In another open-label study,[39] 16 of 18 youths (88%) with bipolar depression or mixed mania improved with lamotrigine alone or as adjunctive therapy, as shown by Clinical Global Impression of Change scores. CDRS-R scores also decreased by ≥ 50% in 11 of 17 who finished the study.

Safety: Severe rash. An age-related association with Stevens-Johnson syndrome may limit pediatric use of lamotrigine. Severe and potentially life-threatening rashes have been reported in 0.8% of children treated with lamotrigine.[40] Discontinue lamotrigine if a rash develops, unless it clearly is not drug-related. Three factors that increase rash risk include:

- co-administering lamotrigine with valproate
- higher-than-recommended initial dosages
- rapid dose titration.[41]

Most rashes appear in the first 8 weeks,[41] though cases can occur after prolonged treatment.

Pediatric dosing. We find no published studies of efficacious dosages and plasma levels of lamotrigine in pediatric bipolar disorder (*Table 4*).[3,9,17] Based on our clinical experience, we recommend starting lamotrigine at 1 to 5 mg/kg/day (1 to 3 mg/kg/day if given with valproate) divided into two daily doses. Watch for rash or skin disorders. Do not exceed the recommended daily dosage by 200 mg in children age <12 or by 350 mg in adolescents.

TOPIRAMATE: LIMITED INFORMATION

Efficacy. Little is known about using topiramate in children and adolescents. A retrospective chart

review[42] of 26 patients with bipolar disorder type I (n=23) or II (n=3) showed adjunctive topiramate to be effective, with response rates of 73% for mania and 62% overall. Topiramate was well tolerated, and no serious events were reported.

A randomized, controlled trial of topiramate for acute mania in youths with type I bipolar disorder[43] was recently halted because of lack of efficacy in adult trials. Preliminary data from 56 of the pediatric patients—analyzed before the study was halted—showed improved YMRS scores. Although results were not statistically significant, the authors suggest topiramate might be effective in treating children and adolescents with bipolar disorder.

Safety: FDA warning. Decreased sodium bicarbonate leading to hyperchloremic metabolic acidosis has been reported in youths treated with topiramate for seizure disorder,[44] leading to an FDA warning to prescribers.[3] Although no monitoring guidelines exist, we recommend baseline and periodic serum bicarbonate measurements and acid-base evaluations during topiramate treatment, especially when adding other antiepileptics.[44]

Other rare but serious reactions include:

- impaired sweat production and resultant hyperthermia[45]
- ophthalmologic symptoms characterized by secondary acute angle closure glaucoma and acute myopia (usually within 1 month of starting treatment)[46]
- sedation and cognitive difficulties.[47]

Body weight. Body weight declined an average 5.8 kg across 8 weeks among 36 bipolar adults using topiramate (mean 176 mg/d).[47] We find that bipolar teens like topiramate because of weight loss, compared with weight gain with divalproex or lithium, but any pediatric weight loss requires monitoring.

Cognitive effects? Reports of "word finding difficulties" with topiramate[47] may suggest cognitive effects. Thus, be very cautious about using this medication in children and adolescents.

Bottom Line

Treating bipolar disorder in children and adolescents is complicated. Presenting symptoms vary, and limited evidence is available to help the clinician choose appropriate medications. Until more is known about mood-stabilizing agents, use them carefully, with frequent monitoring of psychiatric symptoms and potential adverse reactions.

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Related resources

- Kowatch R, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;44(3):213-35.
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- American Academy of Child and Adolescent Psychiatry. Treatment guidelines for childhood psychiatric disorders. www.aacap.org

DRUG BRAND NAMES

Carbamazepine • Tegretol
Divalproex • Depakote
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid, others
Oxcarbazepine • Trileptal
Topiramate • Topamax

DISCLOSURES

Dr. Kloos, Dr. Hitchcock, and Dr. Ronald Weller report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Elizabeth Weller has been a consultant to or received research grants from GlaxoSmithKline, Johnson & Johnson, Novartis Pharmaceuticals Corp., Abbott Laboratories, and Shire Pharmaceuticals.

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