

# Mood Stabilizers in Children and Adolescents

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## ABSTRACT

**Objective:** The efficacy of mood stabilizers in children and adolescents has not been studied adequately. This article will review existing studies and highlight some important issues in designing future studies on these agents. **Method:** Electronic databases including *Medline*, *PsychInfo*, and *CRISP* were searched for data in children receiving compounds that have mood-stabilizing properties in adults. **Results:** Some open clinical data and an extremely modest amount of controlled research data suggest lithium, carbamazepine, and valproate may be effective mood stabilizers in children and adolescents. There are no controlled data on other potential mood stabilizers in children. **Conclusions:** The disorders that may be responsive to mood stabilizers are among the most morbid in child psychiatry. More studies are needed to clarify the efficacy of these compounds in children and adolescents and to provide a rational basis for choosing among them. *J. Am. Acad. Child Adolesc. Psychiatry*, 1999, 38(5):529–536. **Key Words:** psychopharmacology, bipolar disorder, mood stabilizers.

This review examines what is known about the efficacy of mood stabilizers in children and adolescents. Data on the use of these compounds in children address their use in treating bipolar disorder, conduct disorder and attention-deficit hyperactivity disorder, and violent aggression. A number of these compounds are anticonvulsants, but that use is not considered here.

Adolescents suffer from bipolar disorder with a clinical picture much like that seen in adults, making diagnosis relatively straightforward. The course of adolescent bipolar disorder is also similar to that seen with adult bipolar disorder (Carlson et al., 1977; Welner et al., 1977). The diagnosis of bipolar disorder in prepubertal children has received much attention recently and presents a more difficult diagnostic problem (Bowring and Kovacs, 1992). Bipolar depression in prepubertal children is frequently comorbid with externalizing disorders and more often presents in a rapid-cycling or "mixed" picture (Kovacs and Pollock, 1995; Milberger et al., 1995; Wozniak et al., 1995). In the absence of definitive studies in youth, physicians often base their pharmacological treatment decisions on extrapolation of scientific

data from studies in adults. Even assuming that bipolar disorder is a single disorder or group of disorders throughout the lifespan, biological variability of the organism and age-varying pharmacokinetics and pharmacodynamics limit the usefulness of such extrapolations from adult studies. For example, it appears that even though child and adolescent unipolar disorder is very likely the same underlying disorder as adult depression, tricyclic antidepressants may not be as efficacious in children as in adults though selective serotonin reuptake inhibitors may be equally efficacious throughout the lifespan (reviewed in Birmaher et al., 1996). Therefore, even if juvenile bipolar disorder is similar to the adult form of the disorder, we need controlled studies of mood stabilizers in youth and cannot merely extrapolate from adult studies. Because some compounds show sex- and race-related kinetic variations, these issues require investigation. The developmental factors that play a role in these variations need to be studied.

## LITHIUM

In general, lithium is relatively well-tolerated in children. Side effects have been systematically reported in children as young as 3 years of age (Hagino et al., 1995). Lithium is approved by the Food and Drug Administration (FDA) for treatment of bipolar disorder in adolescents who are 12 years of age or older, but not in prepubertal children. Examinations of the relationship between dosage and plasma have been made

Accepted November 11, 1998.

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(Malone et al., 1995; Vitiello et al., 1987; Weller et al., 1987). The distribution and elimination of lithium has been systematically studied and parallels that seen in adults, with some evidence of shorter elimination half-life and higher total clearance in children. Available side effects data are from case reports, from small case series, and from systematic reporting of side effects in small, controlled efficacy studies. Common lithium side effects in children include nausea, diarrhea, tremor, enuresis, fatigue, ataxia (Silva et al., 1992), leukocytosis, and malaise; less commonly seen are renal, ocular, thyroid, neurological, dermatological, and cardiovascular effects. Changes in weight and growth, diabetes, and hair loss are also seen (Rosenberg et al., 1994). Children younger than age 6 may experience neurological effects relatively frequently (Hagino et al., 1995), and in general younger children seem to experience more side effects than do older children (Campbell et al., 1991).

To date, there is only a single published, methodologically sound, double-blind, randomized controlled trial (RCT) of lithium or other mood stabilizers in youth (Geller et al., 1998). In one very small crossover study, lithium was superior to placebo in 2 of 6 children who had lithium-responding bipolar parents (McKnew et al., 1981). In another brief crossover study, lithium appeared better than placebo in a sample of 11 previously lithium-responding children with manic symptomatology (DeLong and Nieman, 1983). In an open study of 10 children, lithium alone appeared efficacious in prepubertal children with psychotic bipolar disorder (Varanka et al., 1988). In another, 2 of 6 children with prepubertal mania or hypomania improved with lithium (Brumback and Weinberg, 1977).

In adolescents, open trials of lithium for bipolar disorder appear to give response rates similar to that seen in adults (DeLong and Aldershof, 1987; Varanka et al., 1988; Youngerman and Canino, 1978). Strober et al. (1990) conducted a naturalistic prospective follow-up study of 37 adolescents treated successfully with lithium for bipolar disorder during hospitalization. Those who discontinued lithium treatment (against advice) were much more likely to relapse than those who continued the medication.

A recent RCT by Geller tested short-term treatment with lithium versus placebo in adolescents with substance dependency disorders and concomitant bipolar disorder. This study was designed as a 2-week, single-blind, placebo washout phase followed by a 10-week,

placebo-controlled, double-blind, short-term treatment study. Twenty-five subjects were enrolled. Those randomly assigned to receive lithium showed significantly better outcome of both their bipolar disorder and their secondary drug dependency than those randomly assigned to placebo (Geller et al., 1998).

There are 2 NIMH-funded ongoing controlled studies of mood stabilizers in adolescents:

1. "Lithium in Hospitalized Bipolar Manic Adolescents" (Vivian Kafantaris, principal investigator) is a study of lithium treatment in the acute manic phase of adolescent bipolar disorder. Enrollment is ongoing, and there have been no examinations of the controlled portion of the data from this study.
2. "Lithium Prophylaxis in Adolescents With Bipolar Illness" (Martin Keller, Michael Strober, and Neal Ryan, principal investigators) is a multisite, placebo-controlled study of lithium discontinuation after 6 months of medication stabilization. This study is ongoing, and interim analyses have not been performed. Because of slower than anticipated recruitment, the design has been changed to that of a discontinuation study from whatever mood stabilizer or combination of mood stabilizers on which the adolescent has been stabilized.

The strategy of lithium augmentation of tricyclic antidepressants is well-established in adult (nonbipolar) major depression (De Montigny et al., 1981). This strategy has not yet been tested in youth by RCT. In 2 uncontrolled studies, approximately 40% of youth inadequately responding to tricyclics showed a favorable response to the combination of tricyclics and lithium (Ryan et al., 1988; Strober et al., 1992).

Open clinical studies have suggested that lithium may be useful in the treatment of aggression in children, especially when seen in those with mental retardation or other neurological disorders (DeLong and Aldershof, 1987), antisocial personality (Schiff et al., 1982), and extreme aggressiveness (Vetro et al., 1985). However, one study was less promising when lithium was used for aggression with hyperactivity (Greenhill et al., 1973).

The 4 double-blind, placebo-controlled studies that have investigated antiaggressive effect of lithium in children and adolescents with conduct disorder have reported mixed results. Campbell and associates (1984, 1995a) found their hospitalized prepubertal subjects to respond better to lithium than placebo in 2 studies. Conversely, Rifkin and colleagues (1997) reported a

negative response in hospitalized adolescents. This study is limited by the very short duration (2 weeks) of the trial. Silva reported statistically negative results in a very small study of outpatients with aggressive conduct disorder (patients receiving lithium appeared clinically improved, but the difference did not approach significance, perhaps because of small sample size) (reviewed by Campbell et al., 1995b; Silva et al., 1991).

#### CARBAMAZEPINE

Carbamazepine (CBZ) is widely used in the treatment of seizures in children, and for this reason its kinetics have been well-studied (Camfield et al., 1992; Cornaggia et al., 1993; Eeg-Olofsson et al., 1990; Liu and Delgado, 1994; Suzuki et al., 1991; Thakker et al., 1992; Yukawa and Aoyama, 1996). From the neurological literature, there are also relatively extensive data on side effects in children and adolescents. The most commonly seen side effects with this agent in children are drowsiness, loss of coordination, and vertigo. More serious side effects reported to the manufacturer over an 11-year period during which 4 million patients were treated included hematological, dermatological, hepatic, and pancreatic effects; 27 cases of aplastic anemia; and 10 cases of agranulocytosis (Pellock, 1987). While CBZ has been used to treat a variety of psychiatric disorders in children and adolescents, it is not labeled by the FDA for psychiatric indications in any age group.

CBZ has demonstrated efficacy in adult bipolar disorder (Post et al., 1996; Stuppaek et al., 1990), and the combination of lithium and CBZ may be superior to lithium therapy alone (Solomon et al., 1996). In adults, CBZ may be superior to lithium alone in "mixed" or rapid-cycling mania (Calabrese et al., 1996a); however, some examinations do not support this (Okuma, 1993). There are no controlled studies and few anecdotal data on CBZ in children, even though it is certainly used as an adjunct to lithium when lithium treatment alone is ineffective in treating childhood bipolar disorder.

As recently reviewed by Silva et al. (1996), there are 29 reports in the world literature examining CBZ in the treatment of behavioral problems or high activity levels in children. Of these, 3 are double-blind, controlled studies (Garcia Belmonte and Pugliese, 1970; Groh et al., 1971; Puente et al., 1973), all of which appeared in the early 1970s, with a total of 53 patients receiving CBZ and 52 receiving placebo (2 of the studies had crossover design). The overall response percentage in

these 3 studies was 71% to the CBZ and 26% to placebo. Diagnostic schemas have changed since these studies were completed, and a majority of subjects in these 3 trials had "abnormal EEGs."

Despite an earlier promising open pilot study by the same group (Kafantaris et al., 1992), in a 6-week, double-blind study of 22 children aged 5 to 12 with conduct disorder who were hospitalized for aggression, CBZ in doses from 400 to 800 mg with serum levels from 5.0 to 9.1  $\mu\text{g/mL}$  was not superior to placebo in reducing aggressive behavior (Cueva et al., 1996).

Side effects may be relatively common with CBZ, in comparison with lithium or placebo (Cueva et al., 1996), and there are several reports of adverse cognitive and behavioral effects with this compound in children (Bhatara and Carrera, 1994; Pleak et al., 1988).

#### VALPROATE

Because of the widespread use of valproate in the treatment of seizures in children, its kinetics in monotherapy, when combined with other anticonvulsants, and in sustained-release forms is well-studied (Battino et al., 1995a; Botha et al., 1995; Brouwer et al., 1992; Cloyd et al., 1993; Kriel et al., 1986; Sugimoto et al., 1996; Yukawa, 1995; Zaccara et al., 1988).

The common side effects of valproate include sedation, nausea, vomiting, appetite/weight gain, tremor, hepatic toxicity, hyperammonemia, blood dyscrasias, alopecia, decreased serum carnitine, neural tube defects, pancreatitis, hyperglycemia, and menstrual changes (Rosenberg et al., 1994). The hepatic toxicity, which may lead to death, appears to occur almost exclusively in relatively young children, especially those younger than 2 years (Bryant and Dreifuss, 1996; Silberstein and Wilmore, 1996).

A specific concern has recently been raised that valproate may induce a metabolic syndrome, characterized by obesity, hyperinsulinemia, lipid abnormalities, polycystic ovaries, and hyperandrogenism, particularly in younger women. In a cohort of Finnish women taking valproate for seizures, 80 of the women who started taking valproate before the age of 20 years had polycystic ovaries compared with 43% of all women taking valproate (Isojarvi et al., 1993). On replacing valproate with lamotrigine in 16 women, Isojarvi et al. (1998) found the severity of this metabolic syndrome to be reduced (suggesting a partial reversibility). The generalizability of their findings to psychiatric populations is

unknown because the reports of this syndrome, so far, are confined to this single cohort with epilepsy.

Divalproex sodium and valproic acid are now frequently used alone or in combination with lithium in the treatment of adult bipolar disorder (Bowden et al., 1994; Post et al., 1996; Solomon et al., 1997). Valproate may be more effective than lithium in adult subjects who have mixed mania (Bowden, 1995; Calabrese et al., 1996a; Swann et al., 1997). Bipolar adults with seizures or other neurological conditions may also preferentially respond to valproate (Stroll et al., 1994).

Several single case reports and small open series suggest efficacy for valproate as a mood stabilizer in adolescents (Whittier et al., 1995). In 3 open studies, addition of valproate to previously ineffective psychotropic treatments in hospitalized adolescents resulted in symptomatic improvement (Papatheodorou and Kutcher, 1993; West et al., 1994, 1995). Strober (1997) examined the clinical course of the mixed manic state treated with valproate compared with a historical control group treated with lithium who were otherwise similar. That study showed superiority of valproate over lithium for the mixed form of mania but no difference in efficacy between the two for classic mania.

In adults, recent controlled data suggest a relationship between trough levels of valproate and clinical response, and the same data suggest that a rapid dose escalation protocol may lead to earlier symptom improvement (Bowden et al., 1996; Keck et al., 1993). There is an open study examining a rapid dose-loading strategy in adolescents (West et al., 1995) suggesting that response may be somewhat slower in adolescents than adults and that serum levels in the morning after the loading dose may be relatively lower in adolescents.

In an open naturalistic examination of divalproex sodium in 10 adolescents with chronic temper outbursts and mood lability, there appeared to be improvement in all 10 subjects and discontinuation of medication appeared associated with relapse with subsequent improvement after restarting medication in 5 of 6 subjects (Donovan et al., 1997).

#### NOVEL TREATMENTS

Other novel anticonvulsants have been suggested to have mood-stabilizing uses in adult bipolar disorder including lamotrigine (Calabrese et al., 1996b; Walden et al., 1996) and gabapentin (Schaffer and Schaffer,

1997; Stanton et al., 1997). For these agents the pediatric data on kinetics are modest (Battino et al., 1995b; Elwes and Binnie, 1996). There are no data on their potential efficacy as mood stabilizers in children or adolescents.

Calcium antagonists including verapamil (Deicken, 1990; Giannini and Loiselle, 1996; Hoschl et al., 1992; Lenzi et al., 1995; Ostow, 1987) and nimodipine (Goodnick, 1995; Grunze et al., 1996; Pazzaglia et al., 1993) have possible efficacy as mood stabilizers. There is little information on the kinetics of these compounds in children (Wagner et al., 1982). There are few data on their potential efficacy as mood stabilizers in children or adolescents.

Neuroleptics may be used as an adjunct to mood stabilizers in the short-term treatment of bipolar disorder in children and adolescents. One case series suggests that clozapine may be helpful when other neuroleptics have failed in this situation (Kowatch et al., 1995). There are no controlled studies systematically assessing neuroleptics and their use in treatment algorithms for child bipolar disorder.

#### DISCUSSION

Overall, there are a modest number of open clinical trials and case reports examining mood stabilizers in children and adolescents but extremely few RCTs. To date, the completed RCTs with even marginally adequate sample size include only:

- A positive study of lithium versus placebo in substance-abusing bipolar adolescents (Geller et al., 1998).
- A positive study of lithium versus haloperidol versus placebo in treating aggression in undersocialized aggressive conduct disorder (Campbell et al., 1984), which was later replicated in a separate sample by the same group (Campbell et al., 1995a) and which contrasts with one negative study (Rifkin et al., 1997).
- Three positive double-blind, controlled studies from the early 1970s of CBZ versus placebo for behavioral problems and high activity levels (Garcia Belmonte and Pugliese, 1970; Groh et al., 1971; Puente et al., 1973), which are limited by diagnostic schema and inclusion of large number of subjects with "abnormal EEGs."
- A negative 6-week, double-blind study of CBZ versus placebo in hospitalized aggressive children with conduct disorder (Cueva et al., 1996).

Recruitment of an adequate sample size has been, perhaps, the most consistent and single most problem-

atic issue in studies of mood stabilizers in children and adolescents. The total pool of potential patients is much smaller than for comparable adult studies. While bipolar disorder most often has onset during adolescence or early adult life, fewer than half of all subjects will have onset during adolescence, so many people who will be candidates for studies of bipolar disorder in adulthood will not have yet had a first episode. A rough calculation suggests that for adolescent studies, one might have (40 years of adulthood/4 years of adolescence)  $\times$  (100% expressed/50% of cases expressed by adolescence) = 20 times more subjects from which to sample for an adult bipolar study than for an adolescent bipolar study. Even meaningful changes in the assumptions (e.g., factoring in changes in reproductive rates, secular increases, etc.) still result in a 5- to 20-fold greater number of subjects in the pool for adult studies of bipolar disorder compared with the pool for child or adolescent studies. Other factors complicating child and adolescent studies include higher rates of refusal for the study (because to participate requires consent/assent from both parent[s] and child, so more people can veto participation) and potentially higher rates of non-compliance after entry. In addition, some managed care health plans do not permit adolescent participation in studies that may result in assignment to a placebo-only medication arm.

Open naturalistic studies demonstrating feasibility and tolerability and suggesting that mood stabilizers may be effective in children and adolescents for bipolar disorder and for other disorders including aggression with conduct disorder/attention-deficit hyperactivity disorder are a necessary first step. While more open data would always be helpful, such open studies do exist and have been published with sufficient numbers of children treated to pave the way for controlled studies of these compounds. The next stage of controlled studies is likely to require multisite studies for sufficient sample size; funding by industry, the National Institutes of Health, private foundations, or a partnership of federal and corporate or private funding sources; working with mental health advocacy groups to change health provider rules and to facilitate recruitment; and guidance by regulators about appropriate study design.

Side effect data are also necessary for the clinician to make correct judgments on how to use these compounds. Important questions about mood stabilizers that could be answered by systematic side effect data on

samples of 100 or fewer children include the cognitive sequelae of mood stabilizers in children and replication and extension of the data on polycystic ovaries with valproate. Available studies suggest that, in general, valproate and CBZ are well-tolerated by the pediatric population with seizure disorder (reviewed by American Academy of Pediatrics Committee on Drugs, 1995), and cognitive effects that interfere with learning at school are rare (Herranz et al., 1988). However, efficacy studies will not provide sufficient data to answer many side effect questions for the following reasons: First, some side effects of great clinical importance may be rare enough never to be encountered in any realistically sized clinical study (e.g., the question of cardiovascular death from desipramine). Second, one cannot adequately extrapolate from relatively frequent but clinically unimportant changes in an organ system to the infrequent but important changes. Similarly, one cannot extrapolate from the rate of side effects seen with high or toxic doses to the rate seen with therapeutic doses. Very large surveys are needed to address important questions such as, What are the rates of hematological or hepatic adverse effects in older children receiving mood stabilizers? Therefore, in addition to efficacy studies, systematic, large-scale, economical systems to collect adverse event data in children are important.

In summary, we believe that the following are of greatest importance in the study of mood stabilizers in children and adolescents:

- There are no systematic studies on the efficacy of any of the mood stabilizers for prepubertal bipolar disorder. This is a priority area given the morbidity and chronicity of this disorder.
- Studies of mood stabilizers for aggression and conduct disorder are few, are small, and have used heterogeneous inclusion/exclusion criteria, making it difficult to know for which populations this approach is useful. Because such disorders are relatively intractable, this area deserves more study.
- The available RCT data and a considerable amount of open clinical data suggest that adolescent bipolar disorder probably responds to the same agents as adult bipolar disorder. However, the RCT data to support this conclusion, as of yet, consist of a single reported study with lithium in substance-abusing bipolar adolescents. Until there are more consistent data, this question cannot be considered settled. In addition, comparative studies examining the efficacy

of these agents, including time to response, have not been undertaken. Given data that valproate may have a quicker onset of action than lithium in bipolar adults (Bowden et al., 1994) and that it can be given in a rapid loading strategy (Bowden et al., 1996; Keck et al., 1993), comparison of active treatments in adolescent bipolar disorder might permit more rational treatment strategies.

- Many adolescents and children with bipolar disorder do not respond to any of the first-line pharmacological treatments. Therefore, studies with novel agents should be extended to this population. In addition, physicians will continue to use combination therapies in the face of either lack of efficacy or delayed onset of efficacy of single agents. Therefore, the resultant drug-drug interactions also deserve systematic study.
- Systematic assessment of frequent and infrequent side effects of these compounds in children with psychiatric disorders is needed. Existent data in the neurological literature do not completely address side effects that may be more frequent in psychiatric populations. For example, CBZ, a tricyclic agent, may induce mania in susceptible children (Bhatara and Carrera, 1994; Myers and Carrera, 1989; Pleak et al., 1988; Reiss and O'Donnell, 1984).
- Adequate kinetic data in children and adolescents are needed on the newer agents to rationally design phase II and phase III clinical trials in this population. Kinetic data need to examine the effects of age, race, sex, hormonal milieu, and nutritional status on metabolism.
- Objective assessments of compliance are particularly important with bipolar and aggressive children and should be included in the design of future RCT studies.
- Development is not a 3- or 4-step process but rather an interplay of a number of developmental processes proceeding at different rates and interacting with each other. Many aspects of development can a priori be expected to influence kinetics and dynamics of these compounds including the sex steroid milieu, hepatic and renal development, changes in binding proteins, changes in distribution compartments, and brain maturation. Better attention to the richness of the development process is needed.

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**Children's Understanding of Sun Protection Behaviours: A Comparative Analysis.** J. Morris, M. Bandaranayake, R. McGee

**Objective:** To investigate awareness of sun protection behaviours in a sample of primary school children in New Zealand. **Methodology:** Information was collected from 824 primary school children in New Zealand using a drawing and writing technique. **Results:** The data revealed a bias towards sunscreen as a method of sun protection compared with other methods such as clothing and the use of shade. Comparisons between results obtained from children resident in Australia and England indicated a greater awareness of sun protection methods amongst the children from Australia and New Zealand compared with those children living in England. **Conclusions:** Children as young as 5 and 6 can describe the consequences of overexposure to the sun, and can illustrate methods of sun protection. Sunscreen is seen as the main method of sun protection. *J Paediatr Child Health* 1998; 34:254-259