April 2003 Volume 8 - Number 4



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## Pediatric Psychopharmacology

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# CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine


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April 2003
Volume 8 - Number 4





*CNS Spectrums* is an *Index Medicus* journal and is available on MEDLINE under the citation *CNS Spectr*. It is also indexed by DIALOG, EMBASE/Excerpta Medica, Lexis-Nexis, OVID, and SilverPlatter.

*CNS Spectrums* is the official journal of the International Neuropsychiatric Association with members in 30 countries.

*CNS Spectrums*®
(ISSN 1092-8529)
is published monthly by
MBL Communications, Inc.
333 Hudson Street, 7th Floor
New York, NY 10013

One year subscription rates:
domestic $120;
foreign $185;
in-training $75.
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# The Use of Mood Stabilizers and Atypical Antipsychotics in Children and Adolescents With Bipolar Disorders

by Robert A. Kowatch, MD, and Melissa P. DelBello, MD


## ABSTRACT

*The clinical use of mood stabilizers and antipsychotics in children and adolescents with bipolar disorders has increased significantly over the past few years. These agents have multiple effects and interactions. This articles reviews the studies that support the use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders and presents information on these agent's pharmacokinetics, dosing, and drug interactions.*

CNS Spectrums *2003;8(4):273-280*


## INTRODUCTION

The clinical use of mood stabilizers and antipsychotics in children and adolescents with bipolar disorders has increased significantly over the past few years, despite the fact that there are few controlled trials in this population. Current clinical practice is to treat mood episodes in children and adolescents with bipolar disorders, much as one would adults with these disorders, using mood stabilizers and antipsychotics.[1-3] It is also common clinical practice to have patients continue on medications for some time following remission, although the optimal length of maintenance treatment remains unclear and available guidelines are based on limited consensus, not controlled trial outcomes. In this article, we will review the studies that support the use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders.

## MOOD STABILIZERS

Several different classes of psychotropic agents have "mood stabilizing" properties including lithium. valproate, carbamazepine, and the newer atypical antipsychotic and antiepileptic agents. Ghaemi[4] recently proposed that for the treatment of bipolar disorders that a mood stabilizer is, "An agent with efficacy in at least one of the three phases of bipolar disorder (acute.mania, acute depression, or prophylaxis), and it should not cause affective switch to the opposite mood state nor should it worsen the acute episode."[4] This definition makes good clinical sense and is useful heuristically when discussing the various psychotropics that have mood stabilizing properties.

### Lithium

Lithium is the oldest mood stabilizer and has the most studies supporting its use for bipolar disorder in adults. Lithium administration has been shown to alter the post-receptor coupling of signal-transducing G-proteins. Through G-proteins, many neurotransmitter receptors are linked to the enzyme phospholipase C, which hydrolyzes the membrane phospholipid phosphatidylinositol biphosphate to produce two-second messengers, diacylglycerol, and inositol triphosphate. Diacylglycerol activates protein kinase C, and inositol triphosphate releases calcium, which acts as a second messenger. Phospholipid phosphatidylinositol biphosphate is synthesized from free inositol. However, lithium blocks inositol monophosphatase, which inhibits neurons from generating free inositol. Therefore, lithium inhibits second messenger pathways.[5,6] Several controlled studies have clearly demonstrated lithium's efficacy in the treatment and prevention of manic episodes in adults.[7] There have been five controlled trials of lithium in bipolar-disordered children and adolescents. Of these five studies, four[8-11] used a crossover design, which is a less than ideal design for an illness that is cyclical in nature. The average number of subjects in each of these studies was 18 and response rates ranged from 33% to 80%, which reflects the heterogeneous samples and methods employed.

In the only well-controlled prospective, placebo-controlled, investigation of lithium in children and adolescents with bipolar disorders (N=25), Geller and colleagues[12] found that after 6 weeks of treatment, subjects treated with lithium showed a statistically significant decrease in positive urine toxicology screens and a significant improvement in global assessment of functioning (46% in the lithium-treated group versus 8% in the placebo group). In this study, the adolescent's diagnosis

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*Disclosures: The authors reports no financial, academic, or other support of this work.*

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of bipolar disorders preceded their substance abuse by several years. This study demonstrated the efficacy of lithium carbonate for the treatment of bipolar adolescents with comorbid substance use disorders, but did not measure the effect of lithium on mood in these adolescents.

### Clinical Use

Lithium is readily absorbed from the gastrointestinal system with peak levels occurring 2–4 hours after each dose. Lithium is excreted by the kidneys and its serum half-life in children and adolescents is estimated to be ~18 hours[13] Weller and colleagues[14] devised a lithium dosage guide for children and adolescents based upon body weight that is useful, accurate and easy to use with outpatients. According to these guidelines, a dose of 30 mg/kg/day in three divided doses will produce a lithium level of 0.6–1.2 mEq/L within 5 days in a 6–12-year-old child. In children, lithium is usually administered 2–3 times/day and after an adequate serum level is reached, it may be administered once in the morning and once at bedtime in a controlled-release preparation. In adolescents, lithium may be administered once daily, usually at bedtime, in a controlled-release preparation. Serum lithium levels in the range of 0.8–1.2 mEq/L are necessary for mood stabilization during treatment of a child or adolescents during a manic episode and it is best to measure serum lithium levels 12 hours after the last dose. It is important to understand that lithium has a very narrow "therapeutic window" and that lithium toxicity can, in fact, be seen at doses close to therapeutic levels. Possible side effects of lithium in children and adolescents include weight gain, nausea, polyuria, polydipsia, tremor, acne, and hypothyroidism.

Baseline studies prior to initiating treatment with lithium should include: general medical history and physical examination; serum electrolytes; creatinine, blood-urea nitrogen and serum calcium levels; thyroid function tests; Electrocardiogram (EKG); complete blood count with differential; and a pregnancy test for sexually active females. Renal function should be tested every 2–3 months during the first 6 months of treatment with lithium carbonate, and thyroid function should be tested during the first 6 months of treatment. Thereafter, renal and thyroid functions should be checked every 6 months or when clinically indicated.

Chronic treatment with lithium can potentially cause hypoparathyroidism so serum calcium levels should be checked once a year. Lithium should be administered cautiously and serum levels monitored carefully in patients with significant renal, cardiovascular, or thyroid disease, or severe dehydration. Drug interactions with lithium are common and patients should be advised not to take any other medications without first consulting with their prescribing physician.

The following medications may increase serum lithium levels: antibiotics (eg, ampicillin and tetracycline), nonsteroidal anti-inflammatories (eg, ibuprofen), antipsychotic agents, propanolol, and selective serotonin reuptake inhibitors (eg, fluoxetine).[15] Lithium should be administered cautiously and serum levels monitored carefully in patients with significant renal, cardiovascular, or

TABLE 1. MOOD STABILIZERS FOR BIPOLAR CHILDREN AND ADOLESCENTS

| Generic Name | US Trade Name | How Supplied (mg) | Starting Dose | Target Dose | Therapeutic Serum Level | Cautions |
|---|---|---|---|---|---|---|
| Carbamazepine | Tegretol | 100, 200 | Outpatients: 7 mg/kg/day 2–3 daily doses | Based on response and serum levels | 8–11 mg/L | Monitor for CYP drug interactions |
| Carbamazepine XR | Tegretol XR | 100, 200, 400 | | | | |
| Lithium | Lithobid | 300 (and 150 generic) | Outpatients: 25 mg/kg/day 2–3 daily doses | 30 mg/kg/day 2–3 daily doses | 0.8–1.2 mEq/L | Monitor for hypothyroidism Avoid during pregnancy |
| Lithium | Eskalith | 300 or 450 CR | | | | |
| Lithium | Cibalith-S | Lithium 5 cc=300 mg | | | | |
| Oxcarbazepine | Trileptal | 150, 300, 600 | 150 mg BID | 20–29 kg 900 mg/day 30–39 kg 1,200 mg/day >39 kg 1,800 mg/day | N/A | Monitor for hyponatremia |
| Valproic Acid | Depakene | 250, syrup | Outpatients: 15 mg/kg/day 2–3 daily doses | 20 mg/kg/day 2–3 daily doses | 90–120 mg/L | Monitor liver functions and for pancreatitis Avoid during pregnancy |
| Divalproex Sodium | Depakote DR | 125, 250, 500 | | | | |
| | Depkote ER | 250, 500 | | | | |

US=United States; CYP=cytochrome P450; XR=extended-release; Li=lithium; CR=controlled-release; N/A=not applicable; DR=delayed-release, ER=extended-release.

Kowatch RA, DelBello MP. *CNS Spectrums*. Vol 8, No 4. 2003.

thyroid disease, or severe dehydration. Adequate birth control measures must be followed in females of childbearing age taking lithium as lithium is associated with an increased rate of cardiac abnormalities.[16]

Table 1 lists the pediatric dosages, target serum levels, side effects, and cautions for some of the mood stabilizers discussed in this article.

### Valproate

Valproate is another mood stabilizing agent which has demonstrated efficacy in adults with bipolar disorders.[17,18] It is a simple branched-chain carboxylic acid, which was first introduced in the United States in 1978 as an antiepileptic agent. Valproate's exact mechanism of action in mood disorders is unclear but appears to involve increased turnover of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) with potentiation of GABAergic functions, blockage of cell firing induced by *N*-methyl-D-aspartate-type glutamate receptors, and attenuation of protein kinase C isoenzymes.[19,20]

A review of the five adult controlled valproate studies for the acute treatment of mania showed an average response rate of 54%.[21] In many of these studies, positive results were obtained even though patients were selected from a population previously refractory to lithium treatment and those characterized by rapid cycling, mixed affective states, and irritability. There have been a number of older case reports and open prospective trials of valproate in children with bipolar disorder and adolescents suggesting its effectiveness.[22-29]

Recently, there have been two prospective trials that have also suggested that valproate may be effective in this population. Kowatch and colleagues[30] compared the efficacy of three mood stabilizers, lithium, valproate, and carbamazepine in the acute phase treatment of bipolar I or II children and adolescents during a mixed or manic episode. In this study, 42 outpatients with a mean age of 11.4 years were randomly assigned to 6–8 weeks of open treatment with either lithium, valproate, or carbamazepine The primary efficacy measures were the weekly Clinical Global Impression (CGI)-Improvement score and the Young Mania Rating Scale (Y-MRS). Using a >50% change from baseline to exit in the Y-MRS scores to define response, the response rates were: 38% for carbamazepine, 38% for lithium, and 53% for valproate ($\chi^2$=0.85, $P$=.60). Each of the three mood stabilizers were well tolerated and no serious adverse effects were seen.

Wagner and colleagues[31] have recently published the results of an open-label study of valproate in 40 children and adolescents (7–19 years of age) with a primary diagnosis of bipolar disorders. This study attempted to follow an open/discontinuation design in which all the patients were started on medication and were then randomized to either placebo or to medication when they improved, but too few subjects participated in the double-blind period to allow for statistical analysis of efficacy. In their initial open-label phase, subjects were given a starting dosage of valproate of 15 mg/kg/day. The mean final dosage was 17 mg/kg/day. Twenty-two subjects (55%) showed a 50% or more improvement in Mania Rating Scale (MRS) scores during the open phase of treatment. Wagner and colleagues[31] concluded that this study provided "preliminary support for efficacy and safety of divalproex in the treatment of acute manic and mixed states of bipolar disorder in children and adolescents."

### Clinical Use

Valproate is readily absorbed from the gastrointestinal system with peak levels occurring 2–4 hours after each dose. But, if valproate is given with meals to decrease nausea, then peak levels may be reached in 5–6 hours. Valproate is highly protein bound, metabolized in the liver and has a serum half-life between 8–16 hours in children and young adolescents.[32] A starting dose of valproate of 15 mg/kg/day in 2–3 divided doses in children and adolescents, will produce serum valproate levels in the range of 50–60 mg/mL. Once this low serum level has been obtained, the dose is usually titrated upwards depending upon the subject's tolerance and response and it is best to measure serum valproate levels 8–12 hours after the last dose. Optimum serum levels among manic adults is between 75–110 mg/mL.[33] A starting dose of valproate of 15 mg/kg/day in 2–3 divided doses in children and adolescents, will produce serum valproate levels in the range of 50–60 mg/mL. Once this low serum level has been obtained the dose is usually titrated upwards depending upon the subject's tolerance and response and it is best to measure serum valproate levels 8–12 hours after the last dose.

Baseline studies prior to initiating treatment with valproate should include general medical history and physical examination; liver function tests; complete blood count with differential and platelets; and a pregnancy test for sexually active females. A complete blood count with differential, platelet count, and liver functions should be checked every 6 months, or when clinically indicated. Possible common side effects of valproate in children and adolescents include nausea, increased appetite, weight gain, sedation, thrombocytopenia, transient hair loss, tremor, and vomiting. Rarely, pancreatitis and liver failure can also occur. Valproate is metabolized in the liver by the cytochrome P450 (CYP) system and has interactions with a number of other medications which also are metabolized by this system. Medications that will increase valproate levels include erythromycin, selective serotonin reuptake inhibitors, cimetidine, and salicylates. Valproate may increase the levels of the following medications: phenobarbital, primidone, carbamazepine, phenytoin, tricyclics, and lamotrigine. Valproate should be administered cautiously and serum levels and liver functions monitored carefully in patients with significant liver dysfunction. Adequate birth-control measures must be followed in adolescent females taking valproate is associated with an increased rate of neural tube defects.

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