

The Bipolar Child Book 24:Bipolar Children DVD Newsletters
Model IEP Resources Conferences
Consultations with Dr. Papolos Consultations with Clinicians Contact

The Bipolar Child Newsletter ***Summer 2001 Vol. 8***

Trileptal: A Promising New Mood Stabilizer

--Demitri and Janice Papolos

If a parent and a doctor were to dream up a wish list mood stabilizer for a child suffering with bipolar disorder, it would be extremely effective without major side effects, it would work against aggression and rage, it would prevent future episodes of illness, it would require no systematic blood draws, and it would not cause weight gain, liver toxicity or aplastic anemia.



An anticonvulsant launched in this country a year ago February (but used in the pediatric epilepsy population since 1990 in Europe), seems to hold a lot of these cards upon early examination, but much is still left to be seen. It is called oxcarbazepine and is marketed in this country by Novartis under the brand name, Trileptal.

Actually, Trileptal is an analogue of Tegretol (carbamazepine). An analogue is structurally similar to another compound, but differs slightly in its composition (such as replacing one atom by another atom of a different element).

Someone in the Ciba-Geigy labs in Switzerland, played around with the carbamazepine compound and added one oxygen molecule to the top of the middle structure. What a difference an oxygen atom can make: Whereas carbamazepine oxidizes in the body into an active metabolite called 10,11 epoxide, oxcarbazepine rapidly converts in the body to 10-monohydroxide derivative (MHD). (Please [click here](http://www.bipolarchild.com/newsletters/metabolism_oxcarb.html) (http://www.bipolarchild.com/newsletters/metabolism_oxcarb.html) to see a figure of the chemical structure and metabolism of oxcarbazepine vs. carbamazepine.) Carbamazepine (Tegretol) is an effective mood stabilizer for bipolar disorder, but it seems that the 10/11 epoxide metabolite is responsible for some of the major problems that can occur with the drug.

As we write in *The Bipolar Child*, "because Tegretol activates certain enzymes in the liver, and this causes the drug itself and many others to be metabolized faster, the serum Tegretol level may drop somewhat after the first month of treatment, requiring increased doses based on blood levels." Therefore, blood levels are needed more frequently in the beginning of treatment and every three months or so afterward. "(Anecdotally, we have heard of many instances when blood levels have dropped--particularly in young children--multiple times with successive increases in dose due to this enzyme induction.)

This induction of the liver enzymes is a result of the 10,11 epoxide metabolite. In contrast, the principal metabolite of Trileptal's (MHD) has little effect on liver enzymes, so that its own serum levels remain fairly constant. Moreover, unlike Tegretol, it is less likely to increase the rate of elimination of many other drugs.

There have been several reports of bone marrow suppression (aplastic anemia) with

Tegretol. While very rare, this is a life-threatening condition. Even less likely are suppression of the formation of blood platelets required for forming blood clots, and white blood cells that fight infection. Therefore, it is good medical practice to have a complete blood cell count regularly at the beginning of treatment and each time the patient develops any signs of easy bruising, and certainly if the triad of fever, sore throat and rash develop in combination.

Evidently because of its different metabolism, Trileptal is much less likely than Tegretol to cause aplastic anemia. In addition, liver toxicity occurs rarely with Tegretol, but is unknown with Trileptal.

Although Trileptal has less risk of drug-to-drug interaction than Tegretol, it can increase the rate of elimination, and reduce the effectiveness of some drugs--notably oral contraceptives (parents of adolescents, please make note!) and one calcium channel blocker, in particular, Felodipine. Therefore, Trileptal may be safely combined with Lamictal, Depakote, and lithium, as well as with antidepressants and antipsychotic medications.

Sounds great so far, but you must be thinking: What are the side effects of Trileptal and how well does it work?

The Side Effects

Adverse side effects that may occur early in treatment with Trileptal are sleepiness (somnolence), headache, dizziness, double vision, ataxia (unsteadiness), vomiting, rash, and abdominal pain. Most of these side effects--should they occur--recede as the body adjusts to the drug in a few weeks. We have heard of a case of sun sensitivity caused by the drug (not surprising because Tegretol can cause this also).

There is a drop in sodium levels (hyponatremia) in 3% of those taking Trileptal. Therefore, a baseline lab test should be done on all patients before the drug is started, and children with sodium levels below 135 mEq/L should be watched more closely. Hyponatremia is rare in children, but teenagers who may ingest diuretics surreptitiously for weight loss are at risk, and this should be explained to them at the beginning of treatment.

Hyponatremia can be treated easily and it is recommended as a general practice that every fourth drink should be a sodium-containing one such as milk or Gatorade. Milk has 125 grams of sodium in an 8-ounce glass, and Gatorade has 115 mg of sodium in an 8.45-ounce juice box.

Symptoms of hyponatremia include not passing much urine, headache, confusion, tiredness, and, if very severe, seizure and coma. Because Trileptal has been shown to be very effective in the treatment of partial seizures, it is FDA-approved as a monotherapy for epilepsy in adults, and approved for children age 4 and older as an add-on anticonvulsant. Therefore, we already have studies showing its safety in the pediatric population.

How Well Does Trileptal Work in Bipolar Disorder?

Several studies have evaluated the effectiveness of Trileptal in acute mania. In 1983, Dr. Hinderk M. Emrich of the Max Planck Institute in Munich performed a double-blind, placebo-controlled study using oxcarbazepine, and found an average change of 50% in the mania scales was achieved by the use of this medication. As a consequence of these findings, Ciba-Geigy of Basel organized two multi-center studies using oxcarbazepine. One compared oxcarbazepine with the antipsychotic drug, haloperidol (Haldol). After two weeks, both treatments (haloperidol and oxcarbazepine) were about equally effective in the 58-patient study, on the basis of decreasing mania-scale scores.

Another international study compared the anti-manic effects of oxcarbazepine to lithium. Again, after a two-week period, the drugs were found to have about equal efficacy for the treatment of acute mania.

This past May, Michael Reinstein, M.D., an Assistant Professor of Psychiatry at Rush Medical Center in Chicago, presented a poster at the American Psychiatric Association's annual conference, in which he compared Trileptal to Depakote in the treatment of mania and found

them to be indistinguishable in both efficacy and tolerability of side effects in adults.

How well does Trileptal work as a maintenance medication? To date, no drug but lithium has been approved for the prevention of episodes of mania in bipolar disorder, and none is approved for preventing recurrences of bipolar depression specifically. Nevertheless, Tegretol and Depakote are used routinely for these purposes and often seem to do the job well. We have only anecdotal information about prevention of episodes and future stability with the use of Trileptal, but when we asked Dr. Reinstein if he had noticed a preventative quality and how long he saw stability he answered: "We have been using Trileptal a little over a year now and we are very impressed with the stability we've seen in the patients. It has become the first line of treatment in our clinic for our patients with bipolar disorder." Dr. Reinstein also spoke of the effect Trileptal has on the aggressive behaviors of the children he's seen. He said: "When the dose gets high enough, the aggression tends to subside."

We next interviewed Dr. Boris Rubinstein, an Assistant Clinical Professor of Psychiatry and Pediatrics at Columbia University's College of Physicians and Surgeons in New York City because he has treated a number of children with Trileptal. While he doesn't yet use it as a first-line treatment, he told us he was impressed with its mood stabilizing effects and--while cautious-- said that : "In my initial assessment, I am very enthusiastic about Trileptal."

He feels that it may well turn out to be a particularly useful drug for children and spoke of the difficult-to-assess four-year-olds who present with ADHD and a lot of aggressive behaviors. "If these are budding bipolar children, I would feel comfortable starting with Trileptal," he said. Unlike stimulants or antidepressants, this option would not exacerbate a possible bipolar disorder.

Much remains to be learned of Trileptal's efficacy in the treatment of early-onset bipolar disorder, and whether or not it is an effective long-term maintenance treatment, preventing future episodes of cycling. Studies are in the planning stages to answer these questions. It is also important to emphasize that Trileptal is officially recognized by the FDA as an anticonvulsant, and that all use in mania or to prevent recurrences of bipolar disorder are to be considered empirical and "off-label," based on individual clinical decisions by a physician.

Dosing

Trileptal is supplied in 150, 300, and 600 mg tablets scored so that they can be cut in half. In addition, there is a lemon-flavored oral suspension for children who have difficulty swallowing tablets. The liquid preparation is palatable to children (we haven't tasted it, however). It must be shaken well before given to a child. It is supplied at a concentration of 60 mg/ml, or 300 mg per 5 ml teaspoon.

Children are typically started at 300 mg per day--in divided doses--150 mg in the morning; 150 mg approximately 12 hours later. The manufacturer's recommendation is to raise the dosage every 7 days in increments of 300 mg (again the 300 mg increases are best divided into two-a-day half- doses) with a target dose of approximately 900 mg to 1200 mg (some children may require as much as 1500-2400 mg).

The drug reaches a steady state, or stable, concentration in the blood stream after about 4 doses or within two days. One mother whose 11-year-old son was cycling wildly throughout the day (despite his being on Clozaril and Zyprexa) wrote of her son's experience with Trileptal: "At about three weeks, as his dose was 900 mg, we began to see the amplitude of his mood swings diminish. At 6 weeks and 1200 mg, the cycling practically stopped. Since no other medication was added at this time, we're sure the Trileptal smoothed out the cycling pattern."

This young man has now been on the medication for a few months and continues to do well, but--as we said above-- only time will tell if the drug is effective as a long-term maintenance mood stabilizer.

Serum Levels of the Major Trileptal Metabolite (MHD)

A blood test is available to monitor the serum level of MHD (monohydroxide derivative), but the clinical value of this measurement is uncertain. At this point the blood test might be

useful to ensure that an adolescent is taking the medication--more of a measurement of compliance, so to speak, whereas dosing is better guided by clinical response and tolerability by individuals.

The Cost of the Medication

Trileptal is expensive--about \$1.50 for a 300 mg tablet, with only moderate increases in cost-per-pill for larger quantities. If a child takes 1200 mg a day, then a one-month supply will cost about \$150-180. A 2400 mg per day regimen could cost nearly \$300 a month.

As we wrote in *The Bipolar Child* (page 128), "Everyone should comparison shop for medications. The same medication in three drugstores in the same neighborhood can have three very different prices. Also, purchase the largest-size tablet or capsule available, consistent with the dosage prescribed." (A patient taking 1200 mg of Trileptal would pay less for two 600 mg tablets than for four 300 mg tablets.

For families that don't have prescription cards or funds to pay for Trileptal, Novartis runs a program that will supply the medication for free. It can be applied to by the treating physician.

In Conclusion

Naturally, we wish we could give you more information about Trileptal, but we are hopeful that-- for some children--this is a new ally in the fight against this dreadful illness. Because Trileptal's safety profile in children is promising, its levels don't fluctuate due to liver enzyme induction, it requires few blood draws, and it doesn't cause the distress of weight gain, it is a welcome new tool in the psychiatric armamentarium; another option on the table.

We also hope that Trileptal's safety profile will help doctors feel more comfortable making the diagnosis of early-onset bipolar disorder and treating the illness at an earlier age, thus saving the child and the family the chaos this disorder engenders. Perhaps fewer doctors will adopt a "wait-and-see" attitude because they fear possible adverse effects from mood stabilizers.

However, we want to make the point clearly that if your child is doing well on Tegretol, Depakote, lithium, etc. it is unwise to change the regimen because you read about a new drug or supplement. No one drug works for every child, and these other mood stabilizers have known advantages (for instance, there is emerging evidence that lithium has a strong and possibly unique effect against suicidal behavior and is neuroprotective as well). If your child is stable, do nothing to rock that blessed boat.

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The authors wish to thank, once again, Ross J. Baldessarini, M.D. for his abiding interest and expertise.

As a final note, we'd like to point out two non-Trileptal matters: For our Texas readers who have asked when Demitri will be speaking in their state, save October 3rd and 4th, 2001. He will be speaking in Austin under the sponsorship of the Austin Harvard School for two-full-day workshops. Since this is one of only two schools in the country set up specifically to teach children with bipolar disorder and ADHD, we will report on the school's philosophy and curriculum in our next newsletter. (Find out all the details under "Workshops" at <http://www.bipolarchild.com>.)

RESEARCH SURVEY

We are conducting a survey having to do with carbohydrate craving and temperature regulation in children diagnosed with bipolar disorder, and hope that you will find the time to help us in this research effort. The questionnaires shouldn't take more than 15 minutes to complete. In addition, we would ask you to measure your child's body temperature with an oral mercury thermometer at 4 specified times within a 36-hour period.

If interested, below, you will find links to four separate RTF files:

1. [Instructions for the study](http://www.bipolarchild.com/docs/instructions_for_study.rtf) (http://www.bipolarchild.com/docs/instructions_for_study.rtf)
2. [The food cravings and thermoregulation survey with answer sheet](http://www.bipolarchild.com/docs/food_cravings.rtf), (http://www.bipolarchild.com/docs/food_cravings.rtf)
3. [The Bipolar Child Parent Questionnaire](http://www.bipolarchild.com/survey/bipolar_chi_nnaire_v1_2.htm), (http://www.bipolarchild.com/survey/bipolar_chi_nnaire_v1_2.htm)
4. [The body temperature recording sheet](http://www.bipolarchild.com/docs/body_temperature.rtf), (http://www.bipolarchild.com/docs/body_temperature.rtf)

Each of these files has instructions that will hopefully allow you to complete the survey without difficulty.

Please open (1) Instructions for the study first. This document explains the steps that are required to complete the survey.

As soon as the findings are published in the psychiatric literature, we will discuss them in detail in a future newsletter. Thank you so much for considering participating in this study!

Because so many parents signed on after the launch of this newsletter, we'd like to index previous editions. They can all be found under <http://www.bipolarchild.com> if you click on "Info and Articles." To date, we've covered the following topics:

Bipolar Disorder, Co-Occurring Conditions, and the Need for Extreme Caution Before Initiating Drug Treatment - November 1999

Millennium Issue: Aggression and the Overarousal of the Limbic System in Children with Bipolar Disorder - January 2,000

Mood Stabilizers: An Update - March 2000

Night Terrors in Children with Bipolar Disorder - July 2,000

Atypical Antipsychotics: Should They Be Prescribed as a Monotherapy? - October2000

What Can the Amish Teach Us About Early-Onset Bipolar Disorder? - January 2001

The A-Zs of Omega-3's: Essential Fatty Acids in the Treatment of Bipolar Disorder - May 2001

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