

The Bipolar Child Newsletter
March, 2000 Vol. 3
MOOD STABILIZERS

--Demitri and Janice Papolos

While it seemed as if copies of *The Bipolar Child* were never going to arrive in bookstores in January, arrive they did, and we are grateful to all of you who waited patiently and who wrote us your very moving reviews. The book has had seven printings and we've been busy doing quite a bit of publicity and getting the word out about early-onset bipolar disorder. The Oprah Show was received extremely well and we were impressed with the producers who were very sensitive to the children as well as the families. Yesterday we taped an hour-long interview about early-onset bipolar disorder with Dr. Frederick Goodwin for "The Infinite Mind." It will begin airing on NPR stations beginning March 8th, so check your local stations for programming information.

January was a landmark month in many ways. The Child and Adolescent Bipolar Foundation (www.bpkids.org) went live on the World Wide Web at 5:00 p.m on January 18th, and by 12:00 noon the next day, 14,000 people from 30 countries had visited. In its first four weeks, nearly 70,000 sessions were logged on this extremely impressive and informative site, serving almost one million pages. Never again are parents going to feel that they're the only ones dealing with this illness, and never will they find it difficult to gain access to state-of-the-art information about early-onset bipolar disorder. It now exists solidly at the bookstores, in the libraries, and on the Internet.

Despite our extensive "Prescriptions for Treatment" Chapter in the book, the subject of medications is vastly complex and changing rapidly. Our first newsletter warned of the dangers of stimulant and antidepressant drugs for children with bipolar disorder (and from the thousands of emails we've received in the wake of some of the publicity for the book, the problem of children being flipped into manic and aggressive states on these drugs is even more widespread than we'd originally reported). Therefore, we'd like to devote this newsletter to the intricacies of the mainstay of treatment, the mood stabilizers.

Some Points to Keep in Mind:

One of the things that distinguishes the maintenance treatment of children from that of adults is that children are growing and their body mass is increasing constantly, as is their cardiovascular volume. As the volume of their blood increases, a dose that was adequate in September, may not be adequate in January. In other words, the blood levels may be constantly changing and parents and physicians must take into account these physiological changes. Many reports of relapses occurring despite consistency of dosing (no skipped meds) can be blamed on falling blood levels.

The problem with checking blood levels is that many children are extremely sensitive and needle phobic. The very idea of frequent blood tests is a stress to parents and children. However, there is a product developed in Israel called Emla that is available by prescription. It is an anesthetic that can be administered to a child's arm about an hour before the blood draw. One 5 gram tube costs about \$12.50 and is good for one to two blood draws. There is a five-tube kit that costs approximately \$45.00 and a 30 gram tube is also available. The kit comes with an occlusive dressing (it helps the cream penetrate better), but the doctor will give complete directions. Some insurance plans will pay for the prescription, some won't. But if Emla helps the child deal with the uncomfortable situation and produces a less fearful reaction, than it's priceless to the child and the parents who have to deal with the visit to the lab.

Many parents report that they pay their children for each visit to the lab (\$10-\$15 seems to be the going rate), or plan a special treat afterwards to brace them for the experience and so they associate some pleasant things with it.

So, how often should blood levels of lithium, Depakote, or Tegretol, be taken? In the beginning of course, more frequent blood levels will be required, and while it used to be thought that the levels need checking only twice a year or so after stabilization, physicians are beginning to recognize that growing children need more frequent testing. One father whose son's levels have been erratic due to his rapid growth and who suffered a hospitalization in the wake of a mood stabilizer dropping below the therapeutic range is having his son tested once a month throughout his growth spurt.

If the child is stable and mood swings seem attenuated, blood draws can be spaced out. But if a parent begins to see a return of old behavior, or increased oppositional behavior, the levels should be checked immediately.

We'll describe dosing schedules and particular problems or concerns with each of the mood stabilizers. Toward the end of this newsletter we'll discuss what constitutes an adequate trial and when it's time to move onto another mood stabilizer if the results are less than desired or the side effects are burdening the child. Parents should be prepared for there to be an extended period of adjusting and trialing medications. It would be nice if the first drug tried was the "magic bullet" but that is not usually the case.

People often ask is one mood stabilizer better than others and how do physicians make the choice for the first trial. The truth is, no studies have shown any of the medications to be superior to the others. In fact lithium may be better in the maintenance part of treatment than any of the other drugs. Everything depends on the child's unique and individual reaction (and, of course, on the doctor's expertise in prescribing and titrating dosages).

We asked New York City psychiatrist, Gianni Faedda, principal author of "Pediatric-Onset Bipolar Disorder: A Neglected Clinical and Public Health Problem" how he makes his initial choice of a mood stabilizer, and he told us that "The only thing that will push me in one direction or the other is a family history that reveals a good response to one of the mood stabilizers (chances are good that there might be a good response in a child with similar genetics) or the fact that something in the medical history would caution me not to use a drug. For instance, if a child has thyroid problems, I would not use lithium which can cause hypothyroidism. "

We'll discuss lithium, the first mood stabilizer, and then, the anticonvulsant drugs, Tegretol, Depakote, Neurontin, Topamax, and Lamictal. The anticonvulsants have been used in the pediatric and adult populations as anti-seizure medications, and are now often prescribed for children with bipolar disorder (although Lamictal has a caveat we shall describe below).

Because we still don't have a lot of information on Gabitril (tiagabine), we'll report on that when we have some good solid data. We will not discuss the side effect profile of each medication because they are all listed in Chapter Four of The Bipolar Child and this newsletter would become hideously long.

Lithium

Lithium is considered the gold standard for the treatment of bipolar disorder in adults, and an estimated 70-80 percent of patients have a positive therapeutic response to it. But there has long been an idea that rapid-cyclers may not do as well on lithium as they do on the anticonvulsant drugs--Tegretol or Depakote and so on.

But is this true for adults and/or children who have such ultra-rapid cycles? Not necessarily. Some children have an excellent response to the drug or to its use in combination with another mood stabilizer.

Very important, there is newly emerging evidence from the research literature that lithium has a strong and possibly unique effect against suicidal behavior in people with bipolar disorder. And this is not true of the other mood stabilizers as far as we know. According to Ross J. Baldessarini, M.D. of Harvard Medical

School "If the antisuicidal side effects are not shared with other mood-altering agents, this may be due to the cerebral serotonin-enhancing properties of lithium, properties that are not known to be associated with anticonvulsants.

Testing Before Treatment

- *Complete medical history
- *Blood tests that include kidney function studies and thyroid-function studies
- *Urinalysis

Dosing

The following chart identifies a typical lithium-carbonate dosing schedule for children under twelve years of age.

DOSAGE (mg)_____

WEIGHT (pounds) 7 A.M. 12 noon 6 P.M. Total Daily Dose

Less than 55 150 150 300 600

55-88 300 300 300 900

88-110 300 300 600 1200

110-132 600 300 600 1500

Range of Effective Levels

Acute episodes may require levels of 0.6 to 1.5 mEq

Maintenance treatment levels in children typically range from 0.6 to 0.85 mEq/liter.

IMPORTANT!

Sudden Discontinuation of Lithium May Be Dangerous

Lithium treatment is associated with an approximately seven-fold reduction of suicide attempts and fatalities in bipolar patients. However, Drs. Ross J. Baldessarini and Leonardo Tondo recently reported statistics from their large Sardinia study and found that discontinuing lithium rapidly after long-term maintenance led to a sharp increase in suicidal risk. The risk increased twenty-fold in the first twelve months than at later times, but was only half as great following slow discontinuation (fifteen to thirty days versus one to fourteen days). These researchers recommend gradually discontinuing mood-stabilizing medications whenever possible, perhaps over several months.

Antidepressants should not be used during this time.

THE ANTICONVULSANTS: TEGRETOL, DEPAKOTE, NEURONTIN, TOPAMAX, LAMICTAL AND GABITRIL

In the 1970s, studies conducted in Japan demonstrated that a drug introduced for the treatment of temporal lobe epilepsy (Tegretol) can be an effective treatment for acute mania and work to prevent future episodes of bipolar illness. Shortly after that, studies about another anticonvulsant, divalproex sodium (Depakote) and valproic acid (Depakene) showed great promise in the treatment of patients who did not respond to lithium.

It's interesting that anticonvulsants would be so effective because bipolar disorder could be perhaps described as a "seizure in the emotional center of the brain." Dr. Timothy Wilens, author of *Straight Talk About Drugs for Kids* has written that "The anticonvulsants work as mood stabilizers by reducing abnormal firing of nerve impulses in the limbic regions (the emotional center) of the brain."

TEGRETOL

Tegretol (carbamazepine) has acute antimanic effects and also acts to prevent future episodes of illness in bipolar disorder. Some studies have reported that Tegretol has antiaggressive properties, something that might make it particularly useful for children with frequent rage attacks.

Testing Before Treatment:

*Complete medical evaluation

*Blood tests to evaluate liver function, blood cell and platelet counts and iron concentration

Dosing:

Younger children between the ages of six to twelve might be started on a dose of 100 mg daily (or 50 mg two times a day if the liquid is used). The dose is typically increased weekly by increments of 100 mg with an initial target dose of 500-600 mg/ml. At this point, the blood level is obtained five to six days after reaching the initial target dose. Further increases would depend on evidence of clinical response, side effects, and achieving a therapeutic level.

Adolescents older than twelve usually start treatment with doses of 200 mg twice a day and the dose is increased weekly by increments of 200 mg. The usual daily maintenance dose is 800 to 1200 mg.

Because Tegretol activates certain enzymes in the liver, and this causes Tegretol itself and many others medications to be metabolized faster, the serum Tegretol level may drop somewhat after the first month of treatment, requiring increased doses based on blood levels. Blood tests are needed more frequently in the beginning of treatment and every three months or so afterward.

Note: the generic form of Tegretol--carbamazepine--seems to be less well formulated than the brand name drug. It seems that some of the generic versions are less well formulated and the tablets tend to fall apart and to be less well absorbed. If a young woman is on oral contraceptives, Tegretol will reduce the effectiveness of the pill. See page 93-94 for a complete list of drug interactions.

Do not store Tegretol in the bathroom cabinet or in any humid area because humidity may cause Tegretol tablets to harden, become less soluble and lose one-third or more of its effectiveness. They should be stored in moisture-proof containers.

Range of Effective Levels:

6 to 12 mg/ml

DEPAKOTE

Many children are prescribed Depakote (divalproex sodium) but all too often we receive med charts from parents or emails reporting that the Depakote dosage was 250-500 mg a day and "it didn't work." Most children will require far higher doses to achieve therapeutic blood levels, and while all children will reach different blood levels at different dosages, it's important to get the right levels and wait a few weeks before making any judgment about the effectiveness of the drug.

Testing Before Treatment

*Medical exam to gauge liver function, blood cell and platelet counts, and serum iron concentrations.

Dosing

Children are often started on a test dose of 125 mg and adolescents on 250 mg, and the doses are gradually increased to obtain a daily target dose of between 1,000-1,200 mg. Some children will require 1,500-2,000 mg a day to maintain an effective Depakote level. Like Tegretol, Depakote increases its own breakdown and the levels will need to be examined after a month on the medication to see if the level has dropped.

Range of Effective Levels

Many children respond best at levels between 80-90 mg/ml, but some require levels of 100 to 125 mg/ml to achieve adequate symptom relief.

NEURONTIN

Neurontin (gabapentin) is an anti-seizure medication that seems to have few side effects except for its potential to cause sedation. It does not cause weight gain. Neurontin can also be used safely with other medications needed by a child or adolescent with bipolar disorder. There are no blood levels to be determined. However, it has a short half-life and must be administered three times a day.

Although only limited studies have been mounted, the initial results are not impressive. Several highly respected clinicians we know find it does not work well as a mood stabilizer when given as a monotherapy (when it is the only mood stabilizer). One study reported by Atul C. Pande, M.D. at the Third international Conference on Bipolar Disorder in Pittsburgh last June examined the use of Neurontin as an add-on to lithium or Depakote versus a placebo add-on and found that the patients taking the placebo actually had a better response.

However, it seems to be useful as an anti-anxiety agent and is definitely useful as a sedating agent for individuals who experience evening or late-night activation.

Dosing

A therapeutic dose seems to be between 900 and 1,800 mg a day, and, as we mentioned above, it must be given in divided doses, three times a day.

TOPAMAX

Topamax (topiramate) is an anticonvulsive drug chemically unrelated to any other anticonvulsant or mood stabilizing medication. It has been reported to control rapid-cycling and mixed bipolar states in patients who have not responded well to Tegretol or Depakote, but its long-term prevention of cycling has not been established.

What makes this drug of particular interest is that it causes no weight gain. In fact, it may reduce the intense food cravings that may occur with other commonly used psychiatric drugs such as Depakote, Risperdal, and Zyprexa. It can also be used as a sedating agent.

Dosing

An initial dose of 25 mg is given once or twice a day and increased by 25 to 50 mg every week. When Topamax is prescribed as an add-on drug with other anticonvulsants, a target dose of 150 to 200 mg is often often enough for mood stabilization, but some children will require higher doses, even up to 400 mg a day. When Topamax is used as a monotherapy--alone--as it is starting to be used-- a target dose of upwards of 200 mg seems to provide mood stabilization.

The blood levels of Topamax can be lowered by Depakote and especially Tegretol, and Topamax may decrease the effectiveness of birth control pills.

LAMICTAL

Lamictal (lamotrigine) is an anti-seizure medication that may have a significant place in the treatment of bipolar disorder. What sets it apart from most the other mood stabilizers is that it seems to have a significant effect on the depressive symptoms of bipolar disorder. The other mood stabilizers work to act to prevent future episodes of depression and mania, but do not work as well on acute depression. This medication might allow doctors to treat the depressive symptoms of bipolar disorder without antidepressants which tend to cause increased cycling or to flip patients into mixed or manic states. However, Lamictal seems to have weaker antimanic effects, and at higher doses--above 175 mg--it can be activating.

There are no blood levels to be taken, and the side effect profile is mild: But as with all things in life, there is no free lunch. As with the sulfa drugs and penicillin--and even some other antiseizure medications-- Lamictal can produce an allergic response that manifests as a rash and, on rare occasions, the rash can be a serious one that signals a life-threatening condition known as Stevens-Johnson Syndrome.

In most cases, the rash is mild, similar to a sunburn and usually clears up after the drug is stopped (many people can resume the drug later and no rash will occur). But let's take a look at some of the newest research concerning Lamictal and serious rash.

A rash is most likely to develop when the dosing schedule starts too high or is increased too rapidly (start low and go slow is the pertinent phrase here). We spoke with Dr. Andrew Stoll of Harvard Medical School who has quite a bit of experience with the drug and he said that he often takes three months to reach the

target dose.

Other cases of rash occurred when Lamictal was given with Depakote--the Depakote doubled the Lamictal levels. Typically the rash occurs in the first eight weeks of treatment.

A study reported in October 1999 in The Annals of Pharmacotherapy reported on 1,050 patients given Lamictal. The article was a retrospective case record survey at five epilepsy centers in the UK. When reserachers examined the cases of patients who started Lamictal at higher doses, the incidence of serious rash was 1.1 percent and of non-serious rash, 7 percent. In 1994, however, the manufacturer of Lamictal issued a recommendation for a lowered starting dose. When the researchers looked at patients' case records which revealed this lower starting dose, there was a significant reduction in the incidence of serious rash: (0 out of 245 patients).

Recently, an unpublished study conducted by dermatologists found that the immunosuppressive drug, Cyclosporine, effectively curtailed 12 out of 12 cases of Stevens-Johnson Syndrome, and we are investigating this further and will provide more information in another newsletter.

Lamictal remains "Black label" for now (it cannot be given to adolescents younger than 16 and is approved only for children with the severe seizure disorder Lennox-Gaston). Reports of its use for bipolar depression are compelling, however, and future studies should decide how helpful a medicine it will be for bipolar disorder.

Dosing

Lamictal should be started at 25 mg for 10 days to two weeks and then increased by 12.5 mg every ten days to two weeks until a target dose of 100-150 is reached.

WHAT CONSTITUTES AN ADEQUATE TRIAL OF A MOOD STABILIZER? AND AT WHAT POINT DO YOU MOVE ON TO THE NEXT?

In attempting to tackle these questions, we need to point out several things:

1) Reports from many clinical researchers indicate that a combination of two mood stabilizers are often necessary to achieve symptom remission. Therefore, partial response does not necessarily mean that the first drug trialed is of no value.

2) If antidepressants have been administered prior to the trial of a mood stabilizer (between one week to three months), or are prescribed at the same time, it will be difficult to judge the effectiveness of the mood stabilizer.

Antidepressants are destabilizing for the majority of children with bipolar disorder. While some clinicians believe that high doses of mood stabilizers will buffer the activating effects of the anti-depressants, this still remains to be established by clinical trials. (The National Institute of Mental Health is currently planning a four-center study that will hopefully answer this question. They will be using Prozac in combination with mood stabilizers for children and adolescents ages 8-18.)

Now the question becomes, how long should a child be kept on a mood stabilizer before it is determined that another choice might better be instituted. Although it has not been objectively established, a reasonable time period to continue a mood stabilizer once a high therapeutic level has been established (and this can take weeks), would be between 5 and 6 weeks.

A decision has to be made by the physician, parents and child if the drug has had any beneficial effects. If so, it might be wise to add another mood stabilizer. If not, the drug should be tapered slowly and another trial should be initiated.

* * * * *

We'd like to close this newsletter with statements from two parents that we quote in The Bipolar Child. The first is from a father and it concerns the multiple drug trials his son had been through before happening upon the right regimen that made all the difference.

I won't go through all the gory details, but suffice it to say "been there, done that." We tried ten different medications in varying combinations with zero luck. Then last spring we were put in a drug study for *****. Within four weeks my son was a different person. Actually, he was coming back to being the kid we always thought he could be. I'm happy to report that he's back in public school and though we still have "moments," we are actually getting to the point where we can get angry at him for all the normal stuff (like:"get your feet off the sofa!") without feeling like we're taking our lives in our hands.

The second is an abbreviated letter from a mother:

After years of tantrums and misbehavior that only another bipolar parent could understand, Micaela has finally been placed on medication that is making a huge difference.

The doctor tapered the existing med (an SSRI) and then started Micaela on Lithobid.

The first week on Lithobid was awful. The SSRI had finally left her system and the lithium hadn't kicked in. Then a powerful change began to take place.

The child was transformed. She can wait for things now. We can say "no" to her. She can accept disappointment. She has stopped teasing and tormenting her sibs. She has been getting along with her sister.

Her behaviors were not part of her personality. She was not suffering from "middle-child syndrome." My husband and I are not bad parents. She was ill, and after many years, countless hours of anguish, many lost friendships, months of lost learning and schoolwork, a lifetime of heartache, she is better.

We wish all of your children that most precious gift--stability.

All best,
Janice and Demitri Papolos

Resources:

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