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Trileptal (oxcarbazepine)

- History
  - Use in treating bipolar disorder dates at least to the 1980's
  - Used in Europe for since prior to 2000
  - Introduced in the US in 2000
- Evidence:
  - Bellino, 2005: safe and effective in pilot study of 17 outpatients with borderline personality disorder.
  - In a preliminary and retrospective study, Trileptal was as effective as valproic acid in the treatment of mood and schizoaffective disorders.
  - Reinstein, 2001: Trileptal vs. Depakote in the treatment of mania in adults—same efficacy and similar tolerability
  - 1990: multicenter, active-comparator 15 day trial for patients with acute mania, 19 patients (mean dose 2400 mg) had improvements similar to 19 patients given Haldol (mean dose 42 mg).
  - Emrich, 1990: 52 patients (mean dose 1400 mg) had improvements similar to 24 patients given lithium (mean dose 1100 mg).
  - Emrich, 1990: 58 patients; efficacy equal to Haldol
  - Emrich, 1983, small, double-blind, on-off-on trial in six patients, 1800-2100 mg/day, helpful in mania.
  - Some evidence of efficacy in adolescents and lack of efficacy in children
    - Wagner et al, 2006: 116 outpatient children with bipolar I disorder manic or mixed episodes, randomized, placebo-controlled; average dose 1515 mg (range 900-2400 mg), median duration treatment 48 days
      - Many dropped out before completion of the trial
      - Trileptal response rate: 34%
      - Placebo response rate: 42%
      - Timetable of improvement:
        - Day 1-7: 43.3% of the total potential improvement that Trileptal will bring by the end of the 28th day
        - Day 8: 55% of the total
        - Day 10: 60% of the total
        - Day 14: 74.5% of the total
        - Day 21: 90% of the total
        - Day 28+: 100% of the total
    - Del Bello et al, 2005: case series
    - Davanzo, 2004: 2 boys with bipolar disorder, 12 and 15 yo, successfully treated with adjunctive Trileptal 900 mg/day and 450 mg/day respectively.
    - Teitelbraum, 2001: Trileptal added to lithium improved symptoms in a 6 yo with bipolar I.
- Mechanisms of action:
  - Blocks voltage-gated sodium channels, enhancing GABAergic transmission.
  - May block serotonin reuptake (leading to increased serotonin).
  - Interacts with potassium channels
  - Blocks high-voltage activated calcium channels
- Pharmacokinetics
  - Rapidly and almost completely absorbed
  - Rapidly metabolized to pharmacologically active metabolite 10-monohydroxy derivative (MHD; 10,11-hydro-10-hydroxy-5H-dibenzazepine-5-carboxamide)
  - Peak levels 4-6 hours
  - Half-life of main compound 1-2.5 hours; half-life of MHD 8-11 hours.
  - Liver metabolism; mild induction of liver enzymes (3A4) and inhibition of 2C19; excreted renally
  - Dose 300-2400 mg/D
  - Effective plasma levels 10-35.
  - Comes in 150, 300, and 600 mg scored tabs and lemon-flavored oral suspension (either 60 mg/mL or 300 mg/5 ml); shake well.
  - In kids, start at 8-10 mg/kg/day (often 150 mg twice-a-day) and titrate to max dose

        - 900 mg/D in kids 20-29 kg
        - 1200 mg/D in kids 29.1-39 kg
        - 1800 mg/D in kids >39 kg
        - Some youth may need up to 2400 mg/day
    - *Drug-drug interactions*
        - *Reduces effectiveness of birth control pills, decreasing blood levels up to 50% (Fattore, 1999*)
            - *May need to switch to higher potency pill*
            - *May need to augment with barrier method*
        - *Can reduce levels of Depakote*

- Side effects/risks
    - lethargy/sedation/sleepiness/fatigue: 37-40% vs. 10.7% placebo; I have not seen such a high degree of these side effects, and when present I've seen it, it's been mild and transient
    - dizziness in youth 28-39% vs. 10.7% placebo; I've seen this on only a couple of occasions and usually only at high doses
    - nausea/vomiting 30-37% vs. 10.7% in placebo; I've seen this on a few occasions, but usually it's been mild and transient
    - abdominal pain
    - poor balance/unsteadiness; I've seen this only once but only at a very high dose
    - headache 31%; I've not seen this yet
    - double or blurred vision 17-26% vs. none placebo; I've seen this only once (in the patient noted above), only at a very high dose
    - rash 10.2% in youth vs. 1.8% placebo; I've seen this twice; went away with cessation of medication
        - less risk than Tegretol
        - 25% of those who developed a rash on Tegretol will develop one on Trileptal
        - very small risk of more serious allergic reaction involving mucous membranes or multiple organs; risk is calculated at 0.5-6 cases/million person-years (or possible as high as 60 cases/million person-years).
    - low sodium 1-3% overall (less risk than Tegretol); elsewhere noted as 23-50% (though vast majority asymptomatic)
        - Rates
            - <135: 24.5%
            - <130: 10.9%
            - <125: 3% (by age: 0.4% in children, 3.8% in adults, 7.3% in elderly)
            - Did not occur in youth < 6
            - Most patients with sodium <125 were also taking sodium-depleting diuretics, and most remained asymptomatic
        - Signs/symptoms
            - Reduced appetite
            - Vomiting
            - Confusion
            - Ankle swelling
            - Headache
            - Tiredness
            - Reduction in urination
            - If very severe, seizures and coma
        - Sodium levels below 135 should be monitored closely
        - Treatment in youth: every 4th drink should be a sodium-containing one such as milk or Gatorade
    - cognitive dysfunction; better cognitive profile than Tegretol, though associated with modest neuropsychological impairment and EEG slowing. Comparative neurocognitive effects of lithium and AED mood stabilizers (Gualtieri and Johnson, 2006): from least detrimental to most: Lamictal>Trileptal>lithium>topamax>Depakote>Tegretol.
    - liver disease/inflammation (less risk than Tegretol)
    - cardiovascular problems (including heart rhythm problems)
    - hair loss
    - weight gain (but clinically not seen so risk may be quite low)
    - preliminary data suggests Trileptal is safe in pregnancy, but:
        - Neural tube defects on 0.5-1% of those exposed

        - Some animal data suggesting risk of congenital malformations
        - Might reduce folate levels
    - not yet associated with agranulocytosis (risk not clear, though thought to be less than Tegretol)
    - a number of other side effects and risks in multiple organ systems.
    - 2010: post-marketing surveillance in UK (looking at safety)
        - 2,243 patient reports analyzed
        - Prescribed most often for seizures, and also for trigeminal neuralgia
        - 73.2% took the medicatin for more than 6 months
        - Hyponatremia noted in 15 cases
            - 13 of 15 case were in females
            - 4 of the 13 had previously experienced hyponatremia on carbamazepine
        - Generally well tolerated in all age groups, including children under 6
        - Most common side effects: (all most likely in the first month)
            - Drowsiness/sedation
            - Nausea/vomiting
            - Malaise/lassitude
            - Dizziness
            - Rash (more in older patients (average age 53) or if used with other antiepileptic medications; 7 of a total of 63 rash reports were considered to be related to Trileptal
        - 1 of 9 reports of heart palpitations thought to be related to Trileptal
        - 1 case of double vision and 2 cases of visual disturbance
        - 5 women were pregnant while on Trileptal; no offspring had morphological defects

Oxtellar XR (oxcarbazepine XR)

- Dosage/administration
    - Single daily dose
    - Empty stomach (1 hour before or 2 hours after meals); food increases peak levels and, as a consequence, side effects
    - Swallow capsules whole
    - Initial dosing plan
        - For adults
            - 600/day for one week
            - Increase by 600 mg/day each week to target dose
        - For youth
            - 8-10 mg/kg/day (not to exceed 600 mg) for one week
    - Higher doses of Oxtellar XR may be needed in conversion from Trileptal
    - Comes in 150 mg, 300 mg, and 600 mg caps
            - Pregnancy can lower the concentration of the active metabolite (10-MHD)
- Side effects
    - Hyponatremia
        - In one trial with 366 adults with complex partial seizures, 3 incidents of hyponatremia (117, 125, and 126)
        - Overall incidence 1.2%
        - Slight shifts from normal to low (less than 135) in 6.5-9.8% vs. placebo rate of 1.7%
        - Symptoms of low sodium include
            - Nausea
            - Malaise
            - Headache
            - Lethargy
            - Confusion
            - Lowered level of consciousness
            - Increase in seizure frequency or severity (in those with seizure disorders)
    - Anaphylactic reaction rare
    - Hypersensitivity reaction
        - Of those who had such a reaction to carbamazepine (Tegretol), 25-30% will also have such a reaction on oxcarbazepine

        - Serious dermatologic raction (including SJS and TEN)
            - Median time of onset 19 days
            - May require hospitalization
            - Very rarely fatal
            - Background incidence rate for these serious reactions (unrelated to oxcarbazepine) is 0.5-6 cases per million-person years
            - Oxcarbazepine increases this risk from 3-10 fold (so up to 1.5-60 cases per million-person years)
        - Multi-organ hypersensitivity
            - Median time to detection 13 days (range 4-60)
    - Suicidal behavior and ideation
        - Rare and controversial
    - Hematologic
        - Pancytopenia rare
        - Agranulocytosis rare
        - Leukopenia rare
    - Percentages (in an epilepsy study)

Dizziness	20% at 1200	41% at 2400	15% placebo
Somnolence	12% at 1200	14% at 2400	9% placebo
Double vision	10% at 1200	13% at 2400	4% placebo
Weakness or lassitude	9% at 1200	10% at 2400	2% placebo
Headache	8% at 1200	15% at 2400	7% placebo
Vision blurred or impaired	7% at 1200	2% at 2400	3% placebo
Vomiting	6% at 1200	15% at 2400	9% placebo
Ataxia or gait problem	6% at 1200	1% at 2400	2% placebo
Balance problems	5% at 1200	7% at 2400	5% placebo
Tremor	5% at 1200	1% at 2400	2% placebo
Nystagmus	3% at 1200	3% at 2400	1% placebo

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 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 armamaterium; 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.