

Titration Guidelines

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Each prescriber will have a different approach to increasing medication when implementing the brain-based treatment. However, these are some suggested guidelines to discuss with your prescriber that in our experience, increase the likelihood of a successful and smoother titration process when treating DMDD. These tips have been largely successful for our community of families, but it's always important to check with your prescriber about what approach is best for your child.

Titration on Anticonvulsants

- 150 - 300 mg increases on Trileptal every 7-10 days are suggested.
 - Stable blood levels are typically achieved at 30-35, or recommended weight-based dosing range of 35-50 mg/kg/day.Once you get closer to therapeutic levels (about a level of 25), you may want to slow down increases to 75-150mg at a time, so you don't go over your target range.
- For those not taking Trileptal, and instead on Vimpat or Lamictal, 25-50 mg increases every 7-10 days. Stable blood levels on Vimpat are typically 10-15, and 10-12 on Lamictal. The recommended weight-based dosing range for Lamictal is 6-10 mg/kg/day.
- Less commonly used anticonvulsants are Tegretol and Keppra (Depakote is NOT recommended, as it does not work as effectively as the others).
- **Anticonvulsants are typically taken twice a day in the morning and evening, 10-12 hours apart.**
- Alternating doses with each increase could help with behaviors (add to morning with 1st increase, add to evening with 2nd increase, etc.).
- **It is normal for the titration process to take some time, often several months to a year, depending on titration dosing and frequency.**

Calculating Anticonvulsant Range Based on Weight

There are formulas you can use to guesstimate the target dose that is appropriate for weight. This range is an estimate of how much they may need to reach stability. **Blood levels are essential**, so you know how the medication is being metabolized. It is also very important to consider behavior and side effects when titrating and adjusting medication accordingly.

Calculating weight-based dosing range for Trileptal at 35-50 mg/kg/day:

- 1. Convert your child's weight to kilograms.**
 - Divide weight in pounds by 2.2 to convert to kg. **Or** you can simply 'Google' it.
 - For example, a child who is 120 lbs. weighs 54.43 kg.
- 2. Multiply their weight in kg by the lower end of the dosing recommendation for Trileptal (35).**
 - In this example, multiply $54.43 \times 35 = 1,905.05$ mg. You can round this result to 1900 mg to get the lower end of your child's estimated range.
- 3. Multiply their weight in kg by the higher end of the dosing recommendation (50).**
 - Similarly, multiply $54.43 \times 50 = 2,721.5$ mg. You can round this result to 2,700 mg.
- 4. Determine your child's estimated dosing range by putting your results together:**

1,900 - 2,700 mg daily of Trileptal would likely be needed for stability for a 120 lb. child. Again, this is just an estimate to be used as a general guide.

- Stability is the metric that will determine your dose. You may find stability at lower than recommended doses. Blood levels and side effects are also important to factor in.

A similar 3-step process can be applied when calculating Lamictal estimated weight-based dosing range. However, the number range is different.

- For example, while the Trileptal range is 35-50 mg/kg/day, Lamictal is 6-10 mg/kg/day. So, the appropriate numbers for each medication need to be properly applied. Please check with your prescriber when calculating the dosing range.

What to Expect

It is normal for irritability to increase when going up on anticonvulsants. If irritability is extreme, slowing down may be indicated. Titrations can be tough but know that mood should eventually improve. The long-term results are often worth the temporary hardship.

- **Anticonvulsants can deplete electrolyte and sodium levels in the body. Hydrating with Gatorade, a similar beverage, or milk is recommended.** Hydration can help offset or prevent side effect issues like dizziness, nausea, or headaches. The key is increasing electrolytes, salt, and water, as well as achieving a balance of these things. Niacinamide (not Niacin) can help offset the nausea. Recommended dosing is 100mg taken with each dose.
- On average, it can take at least 1-2 weeks for the body to adjust following a medication increase. Irritability will often level off within about a week.
- **Temporary side effects can occur.** Some common side effects are dizziness, nausea, headaches, fatigue, or hyperactivity depending on the individual child. Appropriate hydration will often offset some of the physical side effects. Talk with your prescriber about side effects that may arise.

Amantadine/ Frontal Lobe Medication

- **amantadine is typically added when a child is close to stability on the anticonvulsant medication.** In some cases, amantadine can be added sooner, after the anticonvulsant medication is very well tolerated. Reaching a blood level of 25 on the anticonvulsant is typical before adding another medication. This helps to determine the culprit of any side effects or difference in behaviors.
- **amantadine is used to support the frontal lobe, and impacts impulsivity and executive functioning.** It works closely with the seizure medication to achieve stability. Unlike anticonvulsants, amantadine often impacts behavior quickly after being administered, especially once at recommended dosing.
- **amantadine stimulates dopamine in the brain, which children with DMDD respond well to.** Amantadine also stimulates norepinephrine in the brain, so it can aggravate the limbic system before it is stabilized by the anticonvulsant.
 - Sometimes adding amantadine too soon can create irritability and negatively impact the mood. When a therapeutic level of anticonvulsant is achieved, amantadine can perform at its best. Families sometimes see additional improvements in areas like hygiene, social skills, motivation, and focus after reaching therapeutic amantadine levels based on the child's behavior control. They are often pleasantly surprised by the huge impact that Amantadine can make.

Therapeutic amantadine doses: 200-400 mg daily. This is not based on any blood levels, only behavior. It also does not take days or weeks to build up in the system; it has a short half-life. Dosages exceeding 15-

20 mg/kg/day should be avoided due to the possibility of DNA damage in brain cells and development of behavioral deficits that have been demonstrated.

- **amantadine is often increased by 50-100 mg weekly.** More pronounced side effects can occur during titration and/or if increased too quickly. Sometimes amantadine is prescribed in 100 mg capsules. Since these cannot be cut, it may be advisable to request amantadine in tablet or liquid form for initial doses.
- **amantadine should be split into 2 doses daily.** Many families find it most effective to give a higher dose first thing in the morning, and the remainder of the daily dose approximately 6-8 hours apart, but before evening, as this is a daytime-only use when treating frontal lobe. If given in the evening, they will sleep off that dose, essentially wasting it.
- **amantadine has some potential side effects:** trouble sleeping, appetite issues, constipation, and eye-related issues. Psychosis in rare cases, or as a rare side effect for kids with a history of psychosis. Many families find that eye issues (and other side effects) resolve after some time on their own, but at times dose adjustments are needed. Seek an ophthalmologist to rule out medication-induced vision issues. Supplementing with magnesium can help with constipation.
- Side effects can often be mitigated or even eliminated with tweaking. Changing the dosage timing or spacing. Giving before meals or adding cyproheptadine, a recommended appetite stimulator.
- **If amantadine is not tolerated, guanfacine is recommended as a possible alternative. Clonidine can also be an alternative; however, it can cause drowsiness.**
- Some families feel that amantadine and Trileptal alone are enough to tackle a combined diagnosis of DMDD and ADHD. Others find that after reaching stability, adding a low dosage of stimulants helps with focus. Adding a stimulant should not be considered until at therapeutic levels on all medications.

About 25% of kids need an amantadine break. This is not usually something to worry about initially in the process and should only be considered once at therapeutic on all medications. In approximately 25% of individuals, the beneficial effect is lost between 4-8 weeks. This is thought to be due to "receptor exhaustion". This problem, and the corrective intervention for it, was discovered during its use in the treatment of Parkinson's. Suspend administration for 48 hours and then reintroduce at the previously effective dose. If this phenomenon occurs, it will reoccur at the same intervals, requiring repeating these breaks at the same interval as it first occurred. This is best managed by planning the suspension for the closest Sat. and Sun. after week 4, 5, 6, etc. (whichever was the time of effect loss).

- Kids who do need these breaks will exhibit an obvious and noticeable return of impulsive behavior: big change in hyperactivity, impulsivity, focus, sometimes verbal behavior like cussing, physical behavior, refusal, big change in self-care or executive functioning. Sometimes irritability will also increase at times. But the key is seeing a SUDDEN change, not gradual, in this type of behavior.

Kids Respond Differently

In a few cases, families will see little to no improvement while titrating up on an anticonvulsant like Trileptal. This can be discouraging initially. But when they get to a 25-35 blood level on Trileptal and amantadine is added, it is sometimes like a switch is flipped. Other families see some improvement almost immediately on the Trileptal, and little difference with the amantadine. Consider alternatives for the medication that doesn't provide adequate stability.

Antipsychotics

Many families are facing the challenge of weaning off antipsychotic medications, which were unsuccessful in treating their child's DMDD. There are different ways of tackling this issue. **It may be generally advisable to do very slow decreases on the antipsychotic medication while at the same time increasing the**

anticonvulsant. Please talk with your prescriber about making a specific plan for your child to implement an even wean/titration schedule.

VERY SLOW is the way to go when weaning antipsychotics.

- Weaning antipsychotics can produce big behaviors, and sometimes even extreme aggression when taken too quickly. Sometimes children also experience withdrawal side effects.
- Effects of antipsychotics are often seen at least 1-3 months after the medications are completely weaned. The first month off is often the worst. These effects can also depend on how long children were on the medication, and how quickly they were weaned.
- It may be contraindicated to use amantadine and Trileptal while an antipsychotic is still on board. Amantadine stimulates dopamine in the brain, while antipsychotics suppress it. Being on both medications, or reducing antipsychotics too rapidly could increase the risk of [neurological tics](#).

Tweaking and Blood Levels for Anticonvulsant

Children are growing and changing all the time. They are not little adults, and therefore require unique medical care. The brain-based treatment requires tweaking. **Checking blood levels is key.** Someone might ask why this is necessary if everything is going well. Well, as soon as something changes, you will need a blood level and other baseline information to go by.

- **Puberty** can change blood levels and checking levels may be necessary more frequently during this time. The release of hormones can interfere with the medication. Estrogen released during menstruation, for example, is a convulsant that can work against the effects of the anticonvulsant. Puberty is a tough stage with DMDD, so extra monitoring and patience is needed.
- **If an issue arises, blood levels may have changed.** If your child's behavior changes, you may ask if their level is too low or too high. Is an amantadine break needed? Puberty, illness, weight loss or weight gain can impact blood levels. These are some of the questions and issues that arise and having the most current blood level information at hand is critical for knowing whether to go up or down on medications.
- **Symptoms alone are not always reliable.** For example, irritability can have several causes. It often indicates that kids are too low on anticonvulsant blood levels. It can sometimes mean that an amantadine break may be needed; especially when coupled with a big change in impulsivity. It can sometimes even indicate that blood levels are too high, or that an increase was too big or too quick.
- It is generally recommended to get a baseline metabolic panel before starting the process. Some prescribers choose to check blood levels at about the halfway point of the therapeutic range, but this is not always needed for this method. **Once a dose within the recommended weight-based range is reached and behaviors are improving, obtaining anticonvulsant blood levels is recommended.** Blood levels in this context allow you to determine what level is stable for your child. They can also help determine whether there is room to increase or decrease, also considering behaviors and side effects. Once stability is achieved, it will become easy to spot when behavior kicks up again, which is a sign to check levels. **It is recommended to also request sodium levels, metabolic panel, and white blood cell count along with the seizure medication blood levels.**
- **Sometimes small changes in dosing or amount of medication can make a huge impact.**
 - For example, a child is getting headaches despite hydrating with Gatorade. Splitting doses of Trileptal into 3 per day instead of 2 can sometimes correct this problem, although **dosing 3x daily long-term is not recommended.**
 - A small reduction in dosage could help if other interventions are unsuccessful.