Mood stabilizers: Balancing tolerability, serum levels, and dosage

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Mr. B, age 32, was diagnosed with bipolar disorder 10 years ago after experiencing a manic episode that resulted in his first psychiatric hospitalization. He was prescribed quetiapine, 400 mg/d, and remained stable for the next several years. Unfortunately, Mr. B developed significant metabolic adverse effects, including diabetes and a 30-pound weight gain, so he was switched from quetiapine to lithium. Mr. B was unable to tolerate the sedation and cognitive effects of lithium, and the dose could not be titrated to within the therapeutic window. As a result, Mr. B experienced a moderate depressive episode. His current clinician would like to initiate lamotrigine at a starting dose of 25 mg/d. Mr. B has not had a manic episode since the index hospitalization, and this is his first depressive episode.

The term "mood stabilizer" has come to refer to medications that treat a depressive and/or manic episode without inducing the other. In conventional terms, it refers to non-antipsychotic medications such as lithium, divalproex, and lamotrigine. Except for lithium, mood stabilizers are also antiepileptic drugs (AEDs). The role of AEDs for treating psychiatric conditions was discovered after they were originally FDA-approved for treating seizures. Following this discovery, the recommended doses and therapeutic ranges for these agents when applied to psychiatric treatment fell into a gray area.

Every patient is different and requires an individualized treatment plan, but this often leaves the clinician wondering, "How high is too high for this mood stabilizer?" or "My patient is responding well, but could a higher dose be even more effective?" In the case of Mr. B, who has trialed 2 medications with poor tolerability, how high can the lamotrigine dose be titrated to achieve a therapeutic response without adverse effects? The literature on this topic does not provide an exact answer, but does shed some light on key considerations for such decisions.

Which mood stabilizers are recommended?

One of the most recently updated guidelines for the treatment of bipolar disorder was

Practice Points

- **Use the therapeutic levels for lithium and divalproex for safety purposes and as a guide for patient specific therapeutic response**. Treat the patient, and do not focus solely on targeting a level.
- **The maximum recommended dose of divalproex is 60 mg/kg/d**, which greatly exceeds the doses typically used in psychiatric practice.
- **The maximum dose of lamotrigine is 400 mg/d,** but studies have found that lower doses are effective for treating bipolar disorder.

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Table 1

Mood stabilizer dosing strategies and therapeutic serum levels

Agent	Dosing	Therapeutic serum levels	Time to obtain levels
Lithium	Start: 300 mg twice daily to 300 mg 3 times daily Usual dose: 900 to 1,800 mg/d	Depression: 0.4 to 0.8 mEq/L Mania: 0.6 to 1.0 mEq/L	Initial trough level should be obtained no earlier than 5 days after dose initiation or dose changes
Divalproex	Load: 20 to 30 mg/kg/d Maximum dose: 60 mg/kg/d	50 to 125 µg/mL	Initial trough level should be obtained no earlier than 3 days after dose initiation or dose changes
Lamotrigine	Slow titration required[a]: Weeks 1 to 2: 25 mg/d Weeks 3 to 4: 50 mg/d Week 5: 100 mg/d Week 6: 200 mg/d Maximum dose: 400 mg/d	3,000 to 14,000 ng/mL[b]	Therapeutic monitoring not required. If trough level desired, level should be drawn no sooner than 5 days after dose changes[a]

[a]This dosing schedule is for patients not taking interacting medications

[b]Therapeutic drug monitoring is not recommended

Source: References 1-5

Clinical Point

Lithium, divalproex, and lamotrigine are each recommended as first-line options for treating bipolar disorder

released in 2018 by the Canadian Network for Mood and Anxiety Treatments (CANMAT).[1] Lithium, divalproex, and lamotrigine were each recommended as a first-line option for treating bipolar disorder. For lithium and divalproex, the CANMAT guidelines recommend serum level monitoring for efficacy and tolerability; however, they do not recommend serum level monitoring for lamotrigine. Lithium and divalproex each have safety and tolerability concerns, particularly when selected for maintenance therapy, whereas lamotrigine is typically much better tolerated.[1] Divalproex and lithium can cause weight gain, gastrointestinal adverse effects (nausea, vomiting, diarrhea), and tremor. Additional tolerability concerns with lithium include renal toxicity, electrocardiogram abnormalities, hypothyroidism, cognitive impairment, and dermatologic reactions. Divalproex can produce greater levels of sedation and may impact reproductive function (oligomenorrhea or hyperandrogenism). One of the most common adverse effects of lamotrigine is a non-serious rash; however, slow dose titration is necessary to decrease the risk of a serious, life-threatening rash such as Stevens-Johnson syndrome.

Lithium

Lithium continues to be regarded as a gold-standard therapy for bipolar disorder. The exact serum levels corresponding to efficacy and tolerability vary. The Lithiumeter: Version 2.0 is a schematic that incorporates the various levels recommended by different clinical guidelines.[2] The recommended serum levels range from 0.6 to 1.0 mEq/L for mania and 0.4 to 0.8 mEq/L for depression.[2] One of the main issues with lithium dosing is balancing a therapeutic level with tolerability and toxicity. Toxicity may begin when lithium levels exceed 1.2 mEq/L, and levels >2.0 mEq/L can be lethal. Signs of acute toxicity include tremor, headache, arrhythmia, nausea, vomiting, diarrhea, polyuria, and polydipsia. Conversely, chronic lithium use may lead to chronic toxicity as patients age and their physical health changes. Signs of chronic toxicity include ataxia, confusion, renal dysfunction, and tremor. There is no "one size fits all" when it comes to lithium

Table 2

Signs and symptoms of lithium toxicity

Agent	Signs and symptom
Lithium	Worsening of adverse effects such as headache, fatigue, nausea, vomiting, diarrhea, polyuria, polydipsia, tremor, polydipsia, arrhythmia Severe toxicity: seizures, coma, ataxia, nystagmus, myoclonic jerks, confusion, disorientation, cardiac toxicity

Source: Reference 2

Table 3

Strategies for managing adverse effects of lithium and divalproex[a]

Agent	Adverse effects	Management strategies
Lithium	Acne	Decrease dose, conventional dermatologic treatments
	Polydipsia/polyuria	Avoid dehydration, lower the dose, consolidate to bedtime
	Weight gain	Increase exercise, monitor diet
	Intentional hand tremor	Divide dose, change to sustained release formulation, add propranolol
	Gastrointestinal upset (nausea, vomiting, diarrhea)	Take with food, change to sustained release formulation, divide dose
	Lethargy	Consolidate dose to bedtime
	Leukocytosis	Monitor for signs of infection
	Hypothyroidism	Monitor and add thyroid supplementation if indicated
Divalproex	Somnolence/fatigue	Dose at bedtime
	Thrombocytopenia	Lower dose
	Alopecia	Lower dose
	Weight gain	Increase exercise, monitor diet

[a]Because lamotrigine is typically much better tolerated than lithium or divalproex, it is not included in this table

Source: References 1,2

Clinical Point

Toxicity may begin when lithium levels exceed 1.2 mEq/L, and levels >2.0 mEq/L can be fatal

dosing. Individualized dosing is necessary to balance efficacy and tolerability.

Divalproex

Divalproex was initially studied for use as an AED, and its therapeutic levels as an AED are not the same as those indicated for bipolar disorder. Generally, patients with bipolar disorder require a divalproex serum level >50 µg/mL. Ranges closer to 100 µg/mL have been found to be most effective for treating acute mania.[3] A loading dose of 20 to 30 mg/kg/d can be administered to help achieve mood stabilization. Again, efficacy must be balanced against toxicity. The maximum dose of divalproex is 60 mg/kg/d, which is rarely seen in psychiatric practice. Early studies of divalproex found adverse effects greatest in individuals with plasma levels >100 µg/mL. Reported adverse effects included alopecia, weight gain, tremor, and mental status changes.[4]

Lamotrigine

Unlike lithium and divalproex, lamotrigine therapeutic drug monitoring is not common. The accepted therapeutic reference range (TRR) for lamotrigine as an AED is 3,000 to 14,000 ng/mL. Unholzer et al[5] evaluated the dose and TRR for individuals with bipolar disorder treated with lamotrigine. No statistically significant difference in lamotrigine serum levels was found in responders vs nonresponders.[5] Most patients were prescribed ≤200 mg/d; however, some were prescribed higher doses. The maximum dose

Related Resource

- Goldberg JF, Ernst CL. Managing the side effects of psychotropic medications. 2nd ed. American Psychiatric Association Publishing; 2019.

Drug Brand Names

Divalproex sodium/valproic acid • Depakote
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Quetiapine • Seroquel

Clinical Point

The therapeutic window of lamotrigine is less narrow than that of lithium or divalproex

recommended when lamotrigine is used as an AED is 400 mg/d; however, this study furthered the evidence that lower doses tend to be effective in bipolar disorder.

CASE CONTINUED

It has been 3 months since Mr. B was initiated on lamotrigine, and he has since been titrated to his current, stable dose of 100 mg/d. Mr. B is no longer experiencing the sedation he had with lithium and has the energy to commit to an exercise routine. This has allowed him to lose 15 pounds so far and greatly improve control of his diabetes.

Dosage summary

Most available evidence supports dosing lithium and divalproex to effect, typically seen between 0.6 to 1.0 mEq/L and 50 to 125 µg/mL, respectively. Higher plasma levels tend to correspond to more adverse effects and toxicity. Lamotrigine does not have such a narrow therapeutic window. Lamotrigine for psychiatric treatment yields greatest efficacy at approximately 200 mg/d, but doses can be increased if warranted, which could be the case in Mr. B.

Table 1[1-5] (***page 38***) outlines dosing strategies and therapeutic serum levels for lithium, divalproex, and lamotrigine. ***Table 2***[2] (***page 39***) lists signs and symptoms of lithium toxicity, and ***Table 3***[1,2] (***page 39***) describes strategies for managing adverse effects of lithium and divalproex.

References

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