

Bipolar disorder: New strategy for checking serum valproate

Routine monitoring may not be necessary or cost-effective

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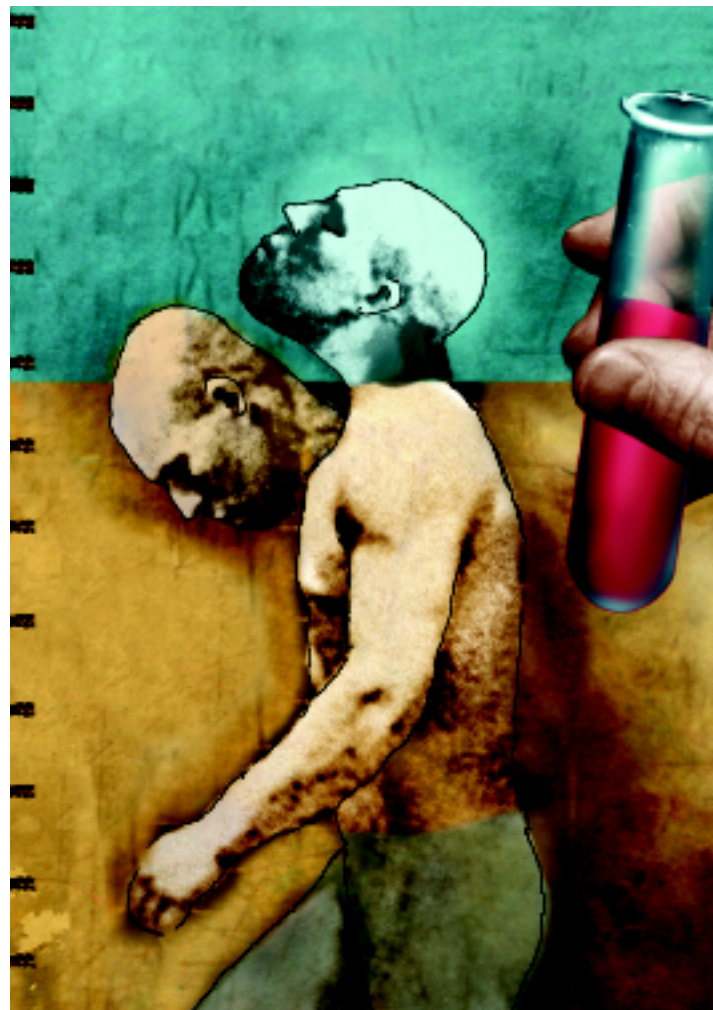
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Valproate's well-accepted therapeutic range for treating epilepsy—50 to 100 mcg/mL—was adopted for bipolar disorder treatment without rigorous evaluation of serum levels and response relationships. Because most literature on monitoring serum valproate refers to its use as an anticonvulsant, you may wonder:

- When should I measure serum valproate in bipolar patients?
- What do serum valproate levels mean in their clinical care?

To answer these questions, we discuss when to monitor serum valproate, whether routinely or in specific situations. We then review studies that



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Table 1

4 situations where serum valproate monitoring may be clinically useful

- To establish** a baseline effective level in individual patients
- To assess** lack or loss of efficacy, including patient adherence
- When drug-drug interactions** increase or decrease valproate clearance (such as with aspirin, carbamazepine, felbamate, or phenytoin)⁵
- When dose-dependent side effects** occur (such as alopecia, elevated liver function, thrombocytopenia, or pancreatitis)

show how serum levels affect valproate’s efficacy and safety in three phases of bipolar disorder management: acute mania, maintenance therapy, and acute depression.

IS MONITORING OVERUSED?

Some neurologists consider serum levels nonessential—and, in some cases, overused—when valproate is used as an anticonvulsant for healthy patients.¹² A multicenter, randomized controlled trial evaluating the impact of antiepileptic drug monitoring on patient outcomes³ supports this notion, at least in part. Serum monitoring did not improve therapeutic outcome, suggesting that patients with epilepsy could be satisfactorily treated by adjusting dosages based on clinical response.

On the other hand, American Psychiatric Association (APA) guidelines for bipolar disorder suggest routine serum monitoring every 6 months along with other hematologic and hepatic assessments, or more frequently if necessary. The APA recommends maintaining serum valproate levels of 50 to 125 mcg/mL when treating:

- acutely manic patients
- outpatients
- the elderly
- patients who are hypomanic or euthymic.⁴

Can monitoring help? Although consensus is lacking on the role and necessity of routine monitor-

ing, serum valproate levels can help when you are seeking the most effective treatment for a bipolar patient (Table 1).⁵ Therapeutic monitoring also may help you assess medication adherence. In fact, monitoring may indirectly enhance adherence when the patient knows you will check serum valproate.

EFFECTIVE LEVELS IN ACUTE MANIA

In one of the first randomized, double-blind, placebo-controlled trials to examine valproate use in adults with acute mania, Pope et al⁶ used the epilepsy reference range to adjust dosages. Patients (n=17) initially received valproate, 750 mg/d, and dosages were then adjusted to serum levels of 50 to 100 mcg/mL. Nineteen patients received placebo. Mean (SD) baseline Young Mania Rating Scale (YMRS) scores for the valproate and placebo groups were 28.2 (5.8) and 28.6 (6.9), respectively.

Patients receiving valproate showed the greatest symptomatic improvement—as indicated by YMRS scores—within 1 to 4 days of achieving a serum level ≥ 50 mcg/mL. Serum valproate for all patients was maintained at >50 mcg/mL, which limits our ability to draw conclusions about a minimum level associated with efficacy.

Minimum threshold for efficacy. In another randomized, double-blind, placebo-controlled study of acute mania, Bowden et al⁷ compared the efficacy of divalproex (n=69) versus lithium (n=36) or placebo (n=74) given for 3 weeks. Patients met criteria for manic disorder using the Schedule for Affective Disorders and Schizophrenia (SADS) and had Mania Rating Scale scores (derived from the SADS) of at least 14.

Those in the divalproex group received 750 mg/d for 2 days, then 1,000 mg/d for 3 days. Dosages were then adjusted to target a serum level

of 150 mcg/mL, unless limited by side effects. Mean serum valproate levels on days 8 and 21 were 77 and 93.2 mcg/mL, respectively. Marked improvement, defined as $\geq 50\%$ reduction in Mania Rating Scale scores, was seen in 48% of the divalproex group, compared with 25% of the placebo group.

The authors then analyzed the relationship between serum valproate levels and clinical response and tolerability.⁸ At day 5, patients with serum valproate ≥ 45 mcg/mL were 2 to 7 times more likely to show 20% or greater improvement in SADS mania subscales (manic syndrome, and behavior and ideation).

This study provided a minimum threshold for valproate efficacy in bipolar mania—45 to 50 mcg/mL—but not a level above which further clinical benefit would not be gained.

Optimum serum ranges. Allen et al⁹ recently conducted a post hoc analysis of pooled intent-to-treat data from three randomized, fixed dose, placebo-controlled studies of divalproex for acute mania. Subjects were stratified into a placebo group (n=171) and six serum valproate ranges:

- ≤ 55 mcg/mL (n=35)
- >55 to 71.3 mcg/mL (n=32)
- >71.3 to 85 mcg/mL (n=36)
- >85 to 94 mcg/mL (n=34)
- >94 to 107 mcg/mL (n=33)
- >107 mcg/mL (n=33).

Valproate was significantly more effective in groups with levels >71 mcg/mL, compared with placebo. Groups with serum valproate of 94 to 107 mcg/mL and >107 mcg/mL also showed greater response than did the group with ≤ 55 mcg/mL.

Effect sizes for the 94 to 107 and >107 mcg/mL groups were -1.06 and -1.07 respectively, similar to 12-point decrease on the YMRS. A median 87 mcg/mL was associated with an effect size of -1.1 .

Loading for rapid response. Patients with acute

Box
2 tips for reliable serum valproate monitoring

When evaluating serum valproate levels—especially for assessing adherence—be careful to:

- obtain blood samples 12 hours after the most recent dose to accurately assess serum trough concentrations
- account for valproate’s saturation of protein binding sites and increased free fraction with increased serum concentration.¹⁶

Valproate clearance is increased when more free drug is available for metabolism, and this may result in disproportionately lower steady-state serum concentrations. Smaller increases in total valproate after dosage increases may be misinterpreted as medication nonadherence.

mania may respond sooner when loading doses are used to attain therapeutic serum valproate levels.

Keck et al¹⁰ examined time to onset of improvement in adults with acute mania (N=19) receiving oral loading doses of valproate (20 mg/kg/d in divided doses for 5 days) to rapidly attain valproate levels ≥ 50 mcg/mL. Ten (53%) patients who received at least 1 loading dose showed a $\geq 50\%$ reduction in MRS scores and the greatest improvement across the first 3 days.

Hirschfeld et al¹¹ also reported that patients’ symptoms began to improve sooner when divalproex was given at 30 mg/kg/d on days 1 and 2, and 20 mg/kg/d on days 3 to 10 (n=20), compared with standard titration (750 mg/d on days 1 and 2, and gradual dose titration on days 3 to 10 [n=20]).

Take samples 12 hrs after the most recent dose for accurate serum trough concentrations

continued



Table 2

For bipolar disorder, suggested serum valproate therapeutic ranges*

	Serum valproate (mcg/mL)		
	Lower level	Upper level	Comments
Acute mania	45 to 50	125	Upper level based on tolerability, not efficacy
Maintenance	75	100	Levels based primarily on retrospective analysis
Acute bipolar depression	Not established	Not established	

* Based on available data

Discussion. In acute mania, evidence suggests that patients with serum valproate \geq 45 to 50 mcg/mL may show greater clinical improvement than patients with lower serum levels. Loading doses may achieve a minimum therapeutic serum level more quickly, yielding faster clinical improvement. A serum level >90 mcg/mL may confer additional benefit.

Although a minimum serum level has been recommended, no data have established a maximum level beyond which further clinical improvement would not be observed.

IN MAINTENANCE THERAPY

What serum valproate levels are most effective for bipolar maintenance therapy? Some evidence is emerging.

Bowden et al¹² compared divalproex (n=187), lithium (n=90), and placebo (n=92) in a 52-week, double-blind, parallel-group study of bipolar adult outpatients who met recovery criteria 3 months after an index manic episode. Divalproex dosages were adjusted to achieve trough serum concentrations between 71 and 125 mcg/mL.

Serum valproate levels >125 mcg/mL have been shown to increase side-effect risk

Mean (SD) and median serum valproate levels were 84.8 (29.9) mcg/mL and 83.9 mcg/mL, respectively. Serum valproate levels significantly correlated with Mania Rating Scale scores. No minimum threshold for efficacy was reported.

Thirteen subjects in the divalproex group were then stratified into 4 categories:

- nontherapeutic (<49.9 mcg/mL)
- low therapeutic (50 to 74.9 mcg/mL)
- medium therapeutic (75 to 99.9 mcg/mL)
- high therapeutic (>100 mcg/mL).

Compared with patients receiving placebo, those in the medium therapeutic group stayed in maintenance therapy significantly longer before discontinuing treatment for any reason or because of mania or depression. No significant differences were seen between the placebo and other 3 valproate groups or between the medium therapeutic and other 3 valproate groups.

Discussion. Serum valproate levels of 75 to 100 mcg/mL may be most effective in preventing subsequent mood episodes with acceptable tolerability. Prospective, longitudinal studies are needed to better establish a therapeutic range for valproate in bipolar maintenance therapy.

IN BIPOLAR DEPRESSION

Little evidence supports a therapeutic serum valproate range for treating acute bipolar depression.

In an 8-week, double-blind study, Davis et al¹⁴ randomly assigned adults with bipolar depression

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to divalproex (n=13) or placebo (n=12). Bipolar depression diagnoses were confirmed using the Structured Clinical Interview for DSM-IV, and patients were required to have a Hamilton Rating Scale for Depression (HRSD) score ≥ 16 .

Valproate was started at 500 mg/d and titrated to serum levels of 50 to 150 mcg/mL. Mean (SD) serum valproate levels at weeks 4 and 8 were 80 (9.3) mcg/mL and 81 (19.2) mcg/mL, respectively. Remission rate (defined a priori as a $>50\%$ improvement and total HRSD score <9) was 46%, which the authors considered more robust than the 43% response rate reported by Sachs et al.¹⁵ In Sachs' 8-week study, the mean (SD) valproate level was 61.5 (42.8) mcg/mL.

Discussion. The relationship between serum valproate and therapeutic efficacy in acute bipolar depression—and the range of levels considered therapeutic—are undefined. For now we recommend that individual patients' clinical response and tolerability guide optimum serum valproate in acute bipolar depression (*Box, page 37*).¹⁶

HIGH LEVELS AND SAFETY

High serum valproate levels may increase the risk and frequency of side effects. For example, serum levels >125 mcg/mL have been associated with:

- increased nausea, vomiting, dizziness, and sedation in acutely manic patients⁸
- weight gain and reduced platelets and white blood cells in patients receiving valproate as maintenance treatment.¹²

Post hoc analysis of divalproex maintenance treatment data did not examine how soon patients discontinued treatment exclusively because of intolerance.¹³

In the loading dose study by Hirschfeld et al,¹¹ patients receiving divalproex, 20 to 30 mg/kg/d, did not experience a higher frequency or severity of side effects compared with patients receiving standard titration. Keck et al¹⁰ also reported minimal valproate-related side effects in their open-label



Serum valproate

Related resources

- ▶ American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002; 159(suppl 4):1-50.
- ▶ Depression and Bipolar Support Alliance. www.dbsalliance.org.

DRUG BRAND NAMES

Carbamazepine • Tegretol, Equetro Felbamate • Felbatol
 Divalproex sodium • Depakote Phenytoin • Dilantin

DISCLOSURES

Dr. Kaneria reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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study. Neither study suggested an upper-limit valproate level associated with increased side effects.

Discussion. Serum valproate >125 mcg/mL has been associated with increased side effects (*Table 2, page 38*), but more studies are needed.

CLINICAL RECOMMENDATIONS

Carefully consider when to monitor serum valproate levels in your patients with bipolar disorder:

- Obtaining routine serum levels can be expensive, and no data support the cost-effectiveness of this approach in bipolar disorder.
- Individualize valproate dosing; a specific

patient's therapeutic range may differ from another's or from those published in the literature or used by a clinical laboratory.

- Monitoring serum valproate levels does not replace the need to adjust dosages based on patients' therapeutic response and tolerance.

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Routine valproate monitoring may not be necessary or cost-effective in all patients with bipolar disorder. Therapeutic serum levels for acute mania and maintenance therapy are emerging, but those for acute bipolar depression are not yet established. Adjust dosages based on patients' therapeutic response and tolerance.

BottomLine