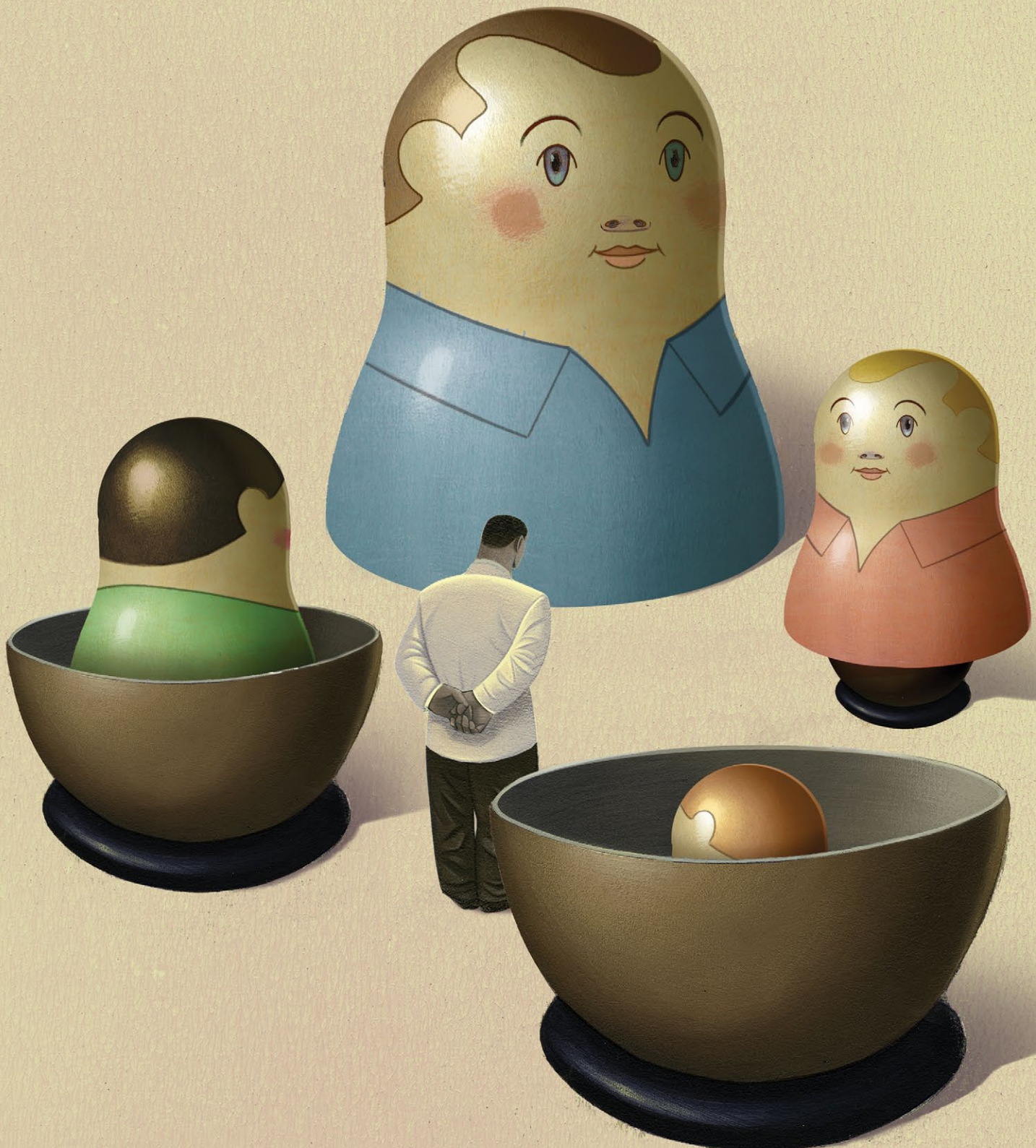
Antiepileptics for psychiatric illness:



Find the right match

Selecting the optimal agent requires knowing each drug's efficacy and safety profile

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JON KRAUSE FOR CURRENT PSYCHIATRY

Although antiepileptic drugs (AEDs) are used to treat a spectrum of psychiatric disorders, in some instances they are prescribed without clear evidence of clinical benefit or safety. When considering prescribing an AED, ask yourself:

- Does the evidence show the drug is efficacious for my patient's disorder or symptoms?
- Which adverse effects are associated with this medication?
- What are the advantages of monitoring the patient's serum drug concentration?

This review provides an evidence-based framework regarding the safe and effective use of AEDs in psychiatric patients.

For which disorders are AEDs effective?

Bipolar disorder. Multiple studies have found that AEDs are efficacious for treating bipolar disorder. Carbamazepine, valproate (divalproex), and lamotrigine have the most evidence supporting their use (***Table 1, page 52***). For an extensive bibliography of studies supporting AEDs for bipolar disorder and other psychiatric illnesses, see this article at CurrentPsychiatry com. Carbamazepine and valproate are FDA-approved for treating acute manic or mixed episodes associated with bipolar I disorder in adults, and may be beneficial for maintenance treatment. Lamotrigine is FDA-approved for maintenance treatment of bipolar I disorder in adults; however, it lacks efficacy for mania and acute bipolar depression.[1] The use of newer AEDs—including gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide—for bipolar disorder is not recommended because evidence is limited or inconclusive.

continued

Antiepileptic selection

Clinical Point

When prescribing carbamazepine, be aware of potential drug-drug interactions with antipsychotics

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Visit this article at CurrentPsychiatry.com for a bibliography of studies supporting antiepileptic use for psychiatric disorders

Table 1

Evidence supporting antiepileptics for mood disorders and schizophrenia

Medication	Bipolar disorder: Mania	Bipolar disorder: Depression	Bipolar disorder: Maintenance	Major depressive disorder	Schizophrenia
Carbamazepine	✓✓✓	✓	✓✓	✓	✓ (aggression, impulsivity)
Lamotrigine			✓✓✓	✓	✓✓ (adjunct to clozapine)
Valproate	✓✓✓	✓	✓✓	✓	✓ (aggression, impulsivity)
Gabapentin			✓		
Levetiracetam			✓		
Oxcarbazepine	✓	✓	✓		
Tiagabine				✓	
Topiramate			✓	✓	✓
Zonisamide			✓		

✓✓✓: strong evidence supporting efficacy; ✓✓: moderate evidence supporting efficacy; ✓: weak evidence supporting efficacy

Source: For an extensive bibliography of studies that support these recommendations, see this article at CurrentPsychiatry.com

Major depressive disorder (MDD). Most studies of AEDs in MDD feature open-label designs with small samples. AEDs might have a role as an augmentation strategy, perhaps for patients with agitation or irritability or who partially respond to antidepressants.[2]

Schizophrenia. Although limited data support the practice, AEDs commonly are combined with antipsychotics to treat patients with schizophrenia.[3,4] Clinicians who prescribe carbamazepine should recognize the potential for drug-drug interactions with antipsychotics (ie, increased metabolism of antipsychotics caused by cytochrome P450 [CYP450] 3A4 induction).

Anxiety disorders. AEDs have a limited role in treating anxiety disorders. These agents may be used as augmentation for patients who exhibit partial response or treatment resistance to recommended agents for anxiety disorders, such as selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines. For patients who cannot tolerate SSRIs or benzodiazepines, AEDs may be alternatives.[5]

Other disorders. AEDs could be used to treat other psychiatric conditions and disorders, including alcohol withdrawal and relapse prevention, benzodiazepine withdrawal, drug dependence and abstinence, obesity, and eating disorders.[4,6,7] A list of suggested AEDs for some of these disorders appears in ***Table 2***. However, these recommendations are based on findings from small randomized controlled trials, open-label trials, or case reports.

What about adverse effects?

A thorough understanding of each AED's adverse effect profile is critical to determine which agent is most suitable for your patient. Factors that may affect the risk of adverse effects include:

- rate of dose escalation
- length of early tolerance development
- rate of increase in and magnitude of peak serum concentrations
- dosing frequency
- pharmacodynamic/pharmacokinetic interactions
- pharmacogenomics.

Cardiovascular effects. Although many AED clinical trials reported "edema" as an adverse effect, peripheral edema specifically has been reported with gabapentin,

Table 2

Off-label use of antiepileptics for various psychiatric disorders

Condition/disorder	Possible medication(s)*
Alcohol withdrawal/relapse prevention	Carbamazepine, topiramate, valproate
Benzodiazepine withdrawal	Carbamazepine, valproate
Binge eating disorder	Topiramate, zonisamide
Bulimia nervosa	Topiramate
Drug dependence/abstinence	Carbamazepine, lamotrigine, topiramate, tiagabine
Generalized anxiety disorder	Pregabalin, tiagabine
Obesity	Lamotrigine, topiramate, zonisamide
Panic disorder	Valproate
Posttraumatic stress disorder	Lamotrigine
Social phobia	Gabapentin, pregabalin

*Based on small randomized controlled trials, open-label trials, or case reports. Further investigation in large systematic trials is needed

lamotrigine, tiagabine, and valproate.[8] Peripheral edema with these agents generally has not been linked to cardiovascular complications in healthy adults. Carbamazepine and pregabalin may cause conduction abnormalities and should be used with caution in patients with underlying electrocardiogram abnormalities.[8]

Chronic carbamazepine use results in elevated plasma homocysteine and serum lipoprotein concentrations, which are biomarkers of cardiovascular disease.[9] If clinically appropriate, switching from carbamazepine to a non-inducing AED (ie, lamotrigine) may ameliorate such effects. Chronic valproate use has been associated with increased plasma homocysteine levels; increases in serum lipoproteins may parallel valproate-induced weight gain.[9]

CNS effects. Common acute neurologic effects of AEDs include somnolence, dizziness, and ataxia. The incidence of these effects vary by agent; gabapentin and zonisamide appear to be the most sedating.[8] However, in general these effects occur at the start of treatment and abate within a few days with continued treatment or dosage reduction. Starting at a low dose and slowly titrating may help prevent neurologic adverse effects.[8] Peripheral neurologic effects—specifically paresthesias—are primarily associated with topiramate and zonisamide and may be attributed to carbonic anhydrase inhibition.[8]

AEDs' primary cognitive effects include impaired attention/vigilance, psychomotor speed, and secondary involvement of other cognitive functions (eg, memory). Whereas carbamazepine and valproate have similar cognitive effects (ie, negative effects on attention, learning, memory, and psychomotor speed), newer AEDs except topiramate may produce fewer cognitive adverse effects (***Table 3, page 62***).[10] Topiramate is associated with the highest rate of cognitive dysfunction, with frequent complaints of decreased concentration and attention, word-finding problems, and/or impaired memory.[8,10]

The FDA recently announced a warning of a risk of aseptic meningitis with lamotrigine.[11] In 40 reported cases, symptoms—headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia, and myalgias—occurred between 1 and 42 days of treatment and typically resolved after lamotrigine was withdrawn. In 15 patients in whom lamotrigine was re-initiated, meningitis symptoms returned quickly and with greater severity.[11]

Dermatologic effects. Skin rashes have been reported with all AEDs; the highest risk is associated with carbamazepine and lamotrigine.[12] Predictors of cutaneous reactions to lamotrigine include:

- high initial dose and rapid escalation
- concomitant valproate use without lamotrigine dosage adjustment

continued on page 62

Clinical Point

Neurologic adverse effects of antiepileptics generally occur at the start of treatment and abate within a few days

continued from page 53

Antiepileptic selection

Clinical Point

A predictor of cutaneous reactions to lamotrigine is concomitant valproate use without lamotrigine dosage adjustment

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Table 3

Comparison of antiepileptics' effects on cognition

Medication	Comparative effect on cognition	Compared with
Carbamazepine	↑	Topiramate
	↔	Oxcarbazepine, tiagabine, valproate
	↓	Gabapentin, lamotrigine, levetiracetam, oxcarbazepine
Lamotrigine	↑	Carbamazepine, topiramate
	↔	Gabapentin
Valproate	↑	Topiramate
	↔	Carbamazepine, oxcarbazepine
Gabapentin	↑	Carbamazepine, topiramate
	↔	Lamotrigine
Levetiracetam	↑	Carbamazepine, pregabalin, topiramate
Oxcarbazepine	↔	Carbamazepine, valproate
Pregabalin	↓	Levetiracetam
Tiagabine	↑	Topiramate
	↔	Carbamazepine
Topiramate	↓	Carbamazepine, gabapentin, lamotrigine, levetiracetam, tiagabine, valproate

↑: positive profile; ↔: similar profile; ↓: negative profile

Source: Reference 10

- young age.[12]

A history of AED-induced rash also increases risk. For example, patients with a history of rash with carbamazepine are at risk for rash with oxcarbazepine because of cross-reactivity.

Any AED-induced skin rash may progress to a fatal reaction, such as toxic epidermal necrolysis or Stevens-Johnson syndrome. Carbamazepine and lamotrigine are most strongly associated with these severe reactions.[12] Patients who exhibit painful rash, fever, enlarged lymph nodes, malaise, and mucosal involvement may be at risk for a more severe disease course.[12] If a patient taking an AED develops a rash, immediately stop the drug and perform a thorough risk-benefit analysis before considering re-initiation.

Hematologic effects. Thrombocytopenia has been reported with carbamazepine, lamotrigine, pregabalin, and valproate. The highest risk is for valproate at doses >50 mg/kg/d or serum concentrations >110 µg/mL in women or >135 µg/mL in men.[13,14] Decreased platelet count is common with valproate, but coagulation dysfunction may not be present until counts fall below 50,000/mL. Carbamazepine is associated with leukopenia, which usually occurs in early treatment and resolves without dosage adjustments; however, this agent carries a black-box warning for risks of agranulocytosis and aplastic anemia. Similar postmarketing findings have been reported with lamotrigine.[8] Baseline hematologic testing and monitoring is recommended.

Hepatic effects. Transient abnormalities in liver function test (LFT) results often have been reported with carbamazepine, valproate, and zonisamide. Valproate has the highest risk of hepatotoxicity, which generally begins within the first 6 months of therapy and does not correlate with serum concentrations.[8] Valproate-induced hepatotoxicity may have acute onset, and hepatic dysfunction may progress despite discontinuing the drug. LFTs are recommended at baseline and regular intervals.[8]

Metabolic effects. AEDs may increase appetite and body weight. Weight gain is common with valproate and pregabalin, but may occur with carbamazepine and gabapentin as well.[8] Weight gain does not appear to be dose-related and may be minimized by diet and exercise. Lamotrigine and levetiracetam do not appear to affect weight, whereas weight loss and anorexia have been reported with topiramate and zonisamide.[8]

Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion have been reported with both carbamazepine and oxcarbazepine; the incidence is higher for oxcarbazepine. For both agents, hyponatremia risk is highest in elderly patients.[12] Valproate—alone and concomitant with topiramate—may elevate ammonia levels, but monitoring generally is necessary only in symptomatic patients. Topiramate and zonisamide increase the risks of hyperchloremic, nonanion gap metabolic acidosis and hypohidrosis; serum bicarbonate should be monitored at baseline and as clinically indicated.[12,15]

Psychiatric effects. Levetiracetam is associated with aggressive behavior, irritability, and increased anxiety and depression, which usually occur soon after drug initiation.[8] Similarly, topiramate use is associated with affective and psychotic symptoms. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and valproate have been associated with a decreased risk of psychiatric adverse effects compared with the overall incidence among AEDs.[8]

An FDA analysis suggested patients receiving AEDs have an elevated risk of suicidal ideation or behaviors, regardless of the indication.[16] However, the data for increased suicidality are better supported for epilepsy patients than for those with a psychiatric diagnosis. The increased risk was noted as early as 1 week after initiating an AED and extended up to 6 months. The findings generally were consistent across demographic subgroups and AEDs.[16] However, a recent study suggests the risk of suicidal acts or violent death is lowest with topiramate compared with gabapentin, lamotrigine, oxcar-

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Valproate-induced hepatotoxicity may have acute onset and hepatic dysfunction may progress despite discontinuing the drug

Antiepileptic selection

Clinical Point

Explain to patients taking topiramate or zonisamide that increasing their fluid intake will significantly reduce kidney stone risk

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Visit this article at CurrentPsychiatry.com for suggested therapeutic serum concentration ranges for carbamazepine and valproate

Table 4

Managing adverse effects of antiepileptics

Medication	Comment(s)
Carbamazepine	Patients screening positive for the variant HLA-B1502 allele are at an elevated risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis. All patients of Asian descent should be screened[22]
Gabapentin	Associated with weight gain, edema, and sedation; no reported effects on liver function tests
Lamotrigine	If therapy has been interrupted for ≥5 to 7 days (≥5 half-lives), restart according to initial dosing recommendations to significantly reduce the risk of rash
Levetiracetam	Appears to have the highest risk of psychiatric adverse effects
Oxcarbazepine	Higher risk of hyponatremia than carbamazepine
Pregabalin	Cases of angioedema have been reported (rare); may cause PR prolongation
Tiagabine	Elevated risk of seizures and status epilepticus when used in non-seizure patients
Topiramate	Increased fluid intake reduces the risk of developing kidney stones
Valproate	Tremor, thrombocytopenia, alopecia, and elevated liver enzymes have been associated with higher valproate doses/serum concentrations
Zonisamide	Avoid use in patients with severe sulfonamide allergy

bazepine, and tiagabine.[17] In patients with bipolar disorder, AEDs might not be associated with increased risk of suicidality and may be protective.[18] All patients treated with AEDs should be closely monitored for emergence of or worsening depression, suicidality, and other behavior changes.[16]

Other effects. Valproate-induced pancreatitis is a rare, life-threatening adverse effect that generally occurs in the first 12 months of treatment and with dose increases.[8] Amylase levels are not strong predictors of valproate-induced pancreatitis because elevations occur in asymptomatic users and normal levels have been reported in affected patients. Valproate also is linked to polycystic ovaries; evidence of this association is stronger in women with seizures than in those with mood disorders.[19]

Secondary to developing metabolic acidosis, both topiramate and zonisamide elevate the risk of developing calcium phosphate kidney stones with long-term use (>1 year).[12,20] The risk appears higher in patients who are male, elderly, or have a personal or family history of kidney stones. Encourage patients taking topiramate or zonisamide to increase their fluid intake because this significantly reduces kidney stone risk.

Rare but potentially fatal angioedema has been reported with oxcarbazepine and pregabalin.[12] History of angioedema or concurrent use of medications associated with angioedema (eg, angiotensin-converting enzyme inhibitors) may confer additional risk.[12]

Pregnancy and lactation. Carbamazepine and valproate have been associated with neural tube, craniofacial, and cardiac defects in the developing fetus.[21] If possible, these agents should be avoided during pregnancy.[21] Despite being teratogenic, carbamazepine and valproate are thought to be safe for women who are breast-feeding.[8] Lamotrigine is associated with mid-facial clefts with first trimester exposure, but is still believed to be a relatively safe option during pregnancy.[2] Because lamotrigine clearance increases as pregnancy progresses, the dosage may need to be increased during pregnancy and decreased after delivery to maintain therapeutic levels. Data are inadequate to assess the safety of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide use during pregnancy and lactation.[8,21]

Table 4[22] provides additional clinical pearls regarding AED adverse effects.

Therapeutic monitoring

Therapeutic serum drug concentration monitoring can help evaluate toxicity, medication adherence, and effects of po-

tential drug-drug interactions. Individual variances in drug metabolism and distribution may affect the correlation between serum concentrations and clinical benefit or toxicity. Therapeutic monitoring can help establish target drug concentrations specific to your patient. The best time to obtain a drug concentration is when your patient is stable or free of most symptoms; this concentration may serve as the patient's "therapeutic" concentration. Although laboratories have set therapeutic concentration ranges for each medication, treatment should focus on addressing your patient's clinical presentation, rather than achieving the laboratory-suggested range.

Carbamazepine and valproate require therapeutic monitoring to prevent adverse effects from supratherapeutic concentrations (see this article at CurrentPsychiatry.com for a ***Table*** listing suggested ranges). The foundation for the therapeutic concentrations of these agents stems from neurology; however, these concentration ranges have been applicable in psychiatry.[23]

Carbamazepine generally requires more frequent monitoring because it has a narrow therapeutic index and relatively high potential for drug-drug interactions. Compared with lower doses, carbamazepine dosing associated with levels >12 µg/mL is more likely to induce toxicity.[23] Carbamazepine autoinduction begins approximately 3 to 5 days after initiation and peaks between 3 to 4 weeks. Therefore, a drop in carbamazepine level from week 1 to week 4 of treatment likely is a pharmacokinetic indicator rather than a sign of nonadherence.

Some acute mania and maintenance bipolar studies have shown a correlation between clinical efficacy and valproate levels.[24] A range of 50 to 125 µg/mL is well-accepted in clinical practice.[24] For some patients, however, symptoms might not resolve until they are above the therapeutic range, but adverse effects are more likely at higher levels.[24]

Because concentrations of newer AEDs—including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide—have not

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Clinical Point

Therapeutic serum drug concentration monitoring can help establish target drug concentrations specific to your patient

Antiepileptic selection

Clinical Point

Carbamazepine and valproate require serum drug concentration monitoring to prevent adverse effects

Related Resources

- McElroy SL, Keck PE, Post RM, eds. Antiepileptic drugs to treat psychiatric disorders. New York, NY: Informa Healthcare USA, Inc.; 2008.
- U.S. Food and Drug Administration. Suicidal behavior and ideation and antiepileptic drugs. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM100190.

Drug Brand Names

Carbamazepine • Carbatrol, Equetro, others
Clozapine • Clozaril
Gabapentin • Neurontin
Lamotrigine • Lamictal, Lamictal XR
Levetiracetam • Keppra, Keppra XR
Oxcarbazepine • Trileptal
Pregabalin • Lyrica
Tiagabine • Gabitril
Topiramate • Topamax
Valproate (Divalproex) • Depakote, Depakote ER
Zonisamide • Zonegram

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

been shown to correlate with therapeutic response, monitoring of serum concentrations is not necessary. However, routine laboratory tests to monitor for adverse effects are recommended.

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Bottom Line

The overall effectiveness of an antiepileptic drug (AED) is paramount when determining its appropriateness for treating a psychiatric disorder. Carbamazepine, lamotrigine, and valproate have the most efficacy data in psychiatry, particularly for bipolar disorder, while newer AEDs are not as well studied. AEDs have varying safety and tolerability profiles, some of which warrant routine serum monitoring.

Table

Therapeutic concentration monitoring for carbamazepine and valproate

Medication	Suggested therapeutic range (trough level)*	Supratherapeutic presentation
Carbamazepine	4 to 12 µg/mL	Ataxia, gastrointestinal upset, drowsiness, dizziness, diplopia, rash
Valproate (divalproex)	50 to 125 µ/mL	Ataxia, nystagmus, tremor, hallucinations

*Values may vary among laboratories

Source: Reference 23