shortchanges patients. Yes, lithium has risks, but its benefits far outweigh those of its competitors as well.

## CONVINCING PATIENTS TO TAKE LITHIUM

Sometimes the doctor is willing, but the patient is not. Often this reluctance has to do with the fact that lithium has long been associated with the diagnosis of manic-depressive illness and thus may carry more stigma than newfangled drugs. In other cases, patients may have taken lithium in the past, often in the hospital, with many side effects. In my experience, the latter scenario usually involves high blood levels of lithium combined with polypharmacy with hefty doses of antipsychotics or other agents. I always try to reason with my patients that they may not have side effects with lithium alone, especially if it is titrated very gradually.

In the case of stigma, I remind my patients that bipolar disorder is bipolar disorder, and the choice of medication does not increase or decrease the severity of the illness. I then recite the benefits of lithium, especially the mortality and cognitive benefits, which are almost always unknown to patients, and then I find them more open to lithium.

Finally, for patients especially attracted to natural treatments, such as herbal medications, owing to their being found in nature and not synthetic, I remind them that lithium is a mineral found in rocks and is part of the table of chemical elements. It is hard to get more natural than that.


# Standard Anticonvulsants

***Essential Concepts***

- Valproate generally is well tolerated, although it can cause gastrointestinal and cognitive side effects, as well as weight gain.
- Despite causing weight gain, valproate does not appear to cause the metabolic syndrome and, in fact, seems to have some beneficial lipid effects.
- Carbamazepine is the only standard mood stabilizer with a low risk of weight gain (unlike lithium and valproate).
- Carbemazepine can be difficult to use owing to its many drug interactions.
- Both agents are indicated by the Food and Drug Administration (FDA) for the treatment of acute mania.
- For mixed episodes, they are more effective than lithium or lamotrigine.
- Both agents have reasonable evidence of efficacy in prevention of mood episodes in bipolar disorder and thus can be considered to be mood stabilizers.
- Both agents have small but replicated evidence of efficacy for acute bipolar depression. This benefit is less well proven than with lithium or quetiapine but more well proven than with lamotrigine or olanzapine.

## VALPROATE

### Indications

Valproate is indicated by the FDA for the treatment of acute mania. A number of studies have shown it to be at least equivalent to lithium or better than placebo, and there are also controlled data indicating that valproate is superior to lithium in treating the acute mixed episode.

## Formulations and Dosing

Valproate, also known in generic form as *valproic acid,* is marketed as divalproex sodium (Depakote). Divalproex appears to possess a somewhat longer half-life and somewhat fewer gastrointestinal side effects than valproic acid. The half-life of valproate usually is greater than 12 hours. Partly owing to many active metabolites with long half-lives, it generally can be dosed once daily, which I strongly recommend for reasons of compliance. It seems that multiple daily dosing has been advocated in epilepsy clinical trials so as to maintain blood levels as stable as possible. While this effect may be relevant to epilepsy, it has not been studied relative to mania. Recently, an extended-release formulation (Depakote ER) was developed that is indicated by the FDA for dosing once daily.

The usual dosage of valproate is about 750 to 1,500 mg per day (range 500 to 2,000 mg per day). It is dosed to a serum therapeutic range of 50 to 120 ng/dL. In the outpatient setting, I begin with 250 mg at night and then increase by 250 mg per day every 5 to 7 days until either it is intolerable or therapeutic-range doses are achieved. In the inpatient setting, it is effective to begin with 500 mg at night and increase by 250 mg per day to 500 mg per day every 1 to 2 days. A standard level for acute and maintenance treatment is in the 60 to 90 ng/dL range. In the definitive clinical trials for acute mania, the mean level was 90 ng/dL or more. It should be remembered that those trials were monotherapy trials (valproate versus lithium versus placebo). If valproate is being used with a neuroleptic, somewhat lower levels may be effective, but levels below 60 to 70 ng/dL probably are insufficient for acute mania. In maintenance treatment, similar levels seem effective, although in my experience levels of 90 ng/dL or higher are not frequently necessary.

**TIP**

In patients with bipolar disorder type II or cyclothymia, some evidence exists that low valproate levels may be sufficient, such as 30 to 60 ng/dL. Some clinicians have the impression that higher levels may worsen depressive symptoms (especially in bipolar disorder type II), which also has been my experience.

Combined with fewer side effects at lower levels and a common reluctance to take mood stabilizers on the part of patients with bipolar disorder type II, such low levels should be offered as a treatment option to those patients. The onus is on clinicians to ensure that patients have type II illness. As noted in Chapter 3, my experience is that many patients labeled as type II in fact have experienced mania and thus have type I illness. In the treatment of acute major depression in bipolar disorder type I, studies support the need for standard serum levels (50 to 120 ng/dL). Low levels should be used only in patients in whom bipolar disorder type I has been clearly ruled out.



One of the major advantages of valproate is its decreased toxicity and large therapeutic index. The difference between a therapeutic level and a toxic level is much larger than with lithium. When levels exceed 100 or 120 ng/dL, toxicity symptoms are not as severe with valproate as with lithium, and usually are associated with severe nausea, sedation, and perhaps dizziness, but not usually serious medical conditions.

## Mechanisms of Action

As with lithium, the psychotropic mechanism of action of valproate is unknown. As with most antiepileptic agents, valproate blocks sodium channels, but this effect is not thought to be relevant to its psychotropic mechanism. Valproate also has moderate GABAergic and mild serotonergic effects, which may provide some antianxiety benefit but are not likely prominent components of its mood effect. It is likely that valproate, like lithium, provides mood-stabilizing effects mainly through second-messenger mechanisms. Recent research found, for instance, that valproate, like lithium, is a potent inhibitor of protein kinase C, an essential ingredient in the second-messenger cascades of many monoamine neuronal systems.

## Side Effects

Overall, valproate is not limited in its side effects, but carefully titrated, it is often well tolerated (Table 15.1). Some of valproate's side effects appear to be, based on clinical experience and available studies, similar in kind and severity to those of lithium. These include weight gain, sedation, cognitive impairment, nausea, diarrhea, and tremor. These side effects generally are dose-related and can respond to lowered serum valproate levels if clinically appropriate. Valproate-induced nausea or weight gain also can respond to

**TABLE 15.1. Standard Anticonvulsants**

| *Drug* | *Effective Dose (mg/day)* | *Side Effects* | *Comments* |
|---|---|---|---|
| Valproate (Divalproex, Depakote, Depakote ER) | 750–1,500 | Gastrointestinal (nausea or diarrhea), sedation, cognitive impairment, weight gain, hair loss, tremor, elevated LFTs, acute pancreatitis, thrombocytopenia, mild anticoagulation, possible PCOS | Reasonably well tolerated, elevated LFTs, risk of pancreatitis, broadly effective, probable PCOS |
| Carbamazepine (Tegretol, (Tegretol, XR, Carbatrol, Equetro) | 600–1,000 | Nausea, diplopia, dizziness, ataxia, sedation, reversible leukopenia, nonserious rash, agranulocytosis, Steven-Johnson syndrome, elevated LFTs; hyponatremia | Multiple nuisance and medically risky side effects, no weight gain |

supplementation with histamine-2 ($H_2$) receptor blockers, such as over-the-counter ranitidine (Zantac). Valproate also can cause hair loss, which may be treatable with supplemental zinc plus selenium used at higher than recommended daily allowance amounts.

## Medical Risks

Medically serious side effects consist mainly of hepatic failure and pancreatitis. Other medical effects, which generally are not potentially lethal, include thrombocytopenia, mild anticoagulation, and possible endocrine abnormalities in women with associated polycystic ovarian syndrome.

Valproate's hepatic effects are usually the most commonly discussed. In reality, potentially lethal hepatic risks are extremely rare in adults. A recent review of mortality owing to hepatitis with valproate found only one reported case in an adult receiving valproate monotherapy, and that patient was 19 years old. Most cases also involved polypharmacy with multiple antiepileptics. Valproate can cause nondangerous elevations of liver function tests (LFTs) in many more persons, but it is important to realize that abnormal LFTs are relatively common and unrelated to the rare and sudden cases of severe hepatitis.



**TIP**

If LFT scores are less than two- to threefold increased, some clinicians continue valproate and simply follow the LFT results. Especially if valproate is uniquely effective for a patient, then mildly elevated but stable LFTs are not a reason for immediate discontinuation of valproate.

In most cases, though, abnormal LFTs continue to rise, and then discontinuation of valproate is prudent. In my opinion, the more important medical risk is acute pancreatitis because this risk is completely unpredictable and can occur at any age. In adults, pancreatitis poses at least as serious a risk as hepatitis. Since there is no way to predict this occurrence, any valproate-treated patient who experiences new abdominal pain should be examined quickly by a physician. If there is any uncertainty, valproate should be held, and amylase and lipase levels should be drawn. If abdominal pain is severe, immediate recourse to an emergency room visit is indicated.

Clinicians sometimes worry about thrombocytopenia, excessively in my view, because reduced platelet levels rarely fall below 50,000/$mm^3$ and even more rarely into the dangerous level of less than 20,000/$mm^3$. Thrombocytopenia is usually mild and stable. This effect would be of concern only in patients with other risks for bleeding. Similarly, the anticoagulant effects of valproate, mediated by clotting factors, are mild and usually clinically limited. Again, patients at risk of even minimal effects, such as those with past cerebral bleeding, should be followed carefully.

Despite causing weight gain, valproate does not seem to lead to increased risk of metabolic syndrome. Indeed, it seems to do the reverse, with evidence in recent randomized data with the ER formulation of decreased total cholesterol levels with valproate compared with placebo. Also, in patients with schizophrenia given antipsychotics such as olanzapine, which

increase lipid levels, coadministration of valproate led to normalization of lipid levels.

The research literature seems to be finding more evidence of a likely association between valproate and polycystic ovarian syndrome (PCOS). PCOS is a condition of elevated concentrations of androgenic hormones in women, with associated cysts on the ovaries and increased infertility. Since valproate causes weight gain, it has been suggested that PCOS really may be a secondary effect of the weight gain rather than a direct effect of valproate. If so, one would expect PCOS to occur as frequently with other anticonvulsants or mood stabilizers, such as lithium, that cause weight gain; yet data from the STEP-BD study indicate that this does not appear to be the case. Other in vivo animal studies also seem to find a direct effect of valproate on increasing androgen activity, unrelated to weight gain.

KEY POINT

Valproate appears to be associated with PCOS, yet clinicians need not avoid valproate in general because of this reason. In persons with other risk factors, such as those with amenorrhea, infertility, and weight gain, the possibility of PCOS should be considered as one factor among many in deciding among mood stabilizers.

## Teratogenicity

Valproate is associated with neural tube defects, as is carbamazepine, and this effect is more frequent than lithium-related teratogenic effects. Some neurologists continue valproate during pregnancy in some patients with epilepsy, but most psychiatric specialists recommend that it be avoided during pregnancy in patients with bipolar disorder.

It also has been shown that fetuses exposed to valproate appear to have slower neurobehavioral development in childhood and lower IQ in middle childhood. Thus valproate appears to have somewhat harmful cognitive effects in children exposed to it during pregnancy.

In my view, despite these drawbacks, the view of some perinatal specialists that one should avoid valproate in general among all young women is an overreaction. All drugs have risks; the clinician's role is not to take one risk and then try to avoid that poor outcome from ever happening, but to



weight all risks against benefits, always starting on the benefit side of the equation (see Holmes' rule in Chapter 5). Thus, for me, what matters in all patients with bipolar disorder, including young women, is to get their mood stably euthymic as long as possible. If it takes valproate, it takes valproate. The longer someone is stably euthymic, the longer he or she will remain so, even after a mood stabilizer is stopped. Young women often stop drinking alcohol for the 9 months of pregnancy; one does not thereby forbid alcohol in all pregnancy-age women. Similar with mood stabilizers such as valproate, if they are otherwise the best choice, I believe that they should be used, and if stable euthymia is achieved, then they can be tapered before a woman decides to conceive. In the rare case, given this approach to using valproate in women, where someone might become pregnant by accident, then addition of folate may help with later first- or second-trimester neural tube risks, or valproate then may be discontinued.

In women who are not stable, not highly noncompliant, or sexually unreliable despite valproate use, it likely should be deemphasized compared with other agents with fewer pregnancy risks, such as lithium, lamotrigine, and antipsychotics. However, valproate should not be avoided in general simply because many persons with bipolar disorder experience sexual impulsivity or are noncompliant when they are symptomatic. It frequently cures them. My point is that if it does not help such individuals after a few months of trial, then long-term treatment carries increased risks of unplanned pregnancy, and in that setting, it often should be removed from the treatment mix.

## Drug Interactions

Valproate is a mild inhibitor of the cytochrome P450 2D6 system, although this effect likely does not lead to much in the way of clinical drug interactions. On the other hand, valproate is very tightly bound to plasma proteins and thus can lead to drug interactions with other agents that are highly protein bound. The most prominent example is a combination with lamotrigine, where blood levels of the latter are markedly elevated in the presence of valproate, leading to a higher rash risk. There are case examples of pedal edema with valproate plus atypical neuroleptics, which may be related to plasma protein binding. Valproate is also a mild inhibitor of certain clotting factors, which can lead to increased bleeding risk with aspirin or other anticoagulants.

## Clinical Effectiveness

### Acute Mania

Valproate is quite effective in mania, equally so whether pure or mixed (unlike lithium, which is half as effective in mixed as in pure manic episodes). Valproate also has the advantage of more rapid onset of action than lithium, with benefit notable in 1 week or so compared with 2 weeks or longer with lithium. Valproate also can be loaded orally, at 20 mg/kg per day, and with that dosing, benefit has been reported within days of initiating treatment. Valproate loading also has been shown to be similar in speed and amount of antimanic effect to haloperidol. I find that valproate loading is especially useful in severely nonpsychotic patients hospitalized because of manic episodes; in psychotic manic episodes or extremely agitated and potentially dangerous manic patients, combination treatment with neuroleptic agents makes sense.

While most clinicians would agree that valproate has many advantages over lithium for acute mania, others seem unclear about the relative benefits of valproate and atypical neuroleptic agents indicated for mania, such as olanzapine. Recently, two double-blind comparisons of olanzapine and valproate were conducted in acute mania. Unfortunately, the studies are not informative because they are not very comparable; despite both being double-blinded, one study dosed olanzapine somewhat low compared with valproate loading, and the other study dosed valproate rather low while dosing olanzapine higher. As might be expected, olanzapine was more effective in the study in which valproate was dosed low, and valproate loading was as effective as olanzapine in the other study. Since we know that valproate loading is more effective than slow titration, these studies suggest that olanzapine is equivalent to valproate loading in the treatment of acute mania. The main differences between the two agents involved side effects: They both caused weight gain, but in both studies, olanzapine caused the most weight gain; olanzapine also caused abnormal lipid profiles, unlike valproate, and one case of fatal diabetic ketoacidosis occurred with olanzapine.

In sum, I tend to prefer valproate for acute mania because it has fewer side effects overall than atypical neuroleptics, and it can be continued in long-term treatment in monotherapy with some evidence of efficacy. No evidence exists for long-term efficacy with atypical neuroleptics in the treatment of bipolar disorder (see Chapter 17). In practice, for hospitalized patients, I recommend combination treatment with valproate or lithium plus atypical neuroleptics.



### Prophylaxis

Frequently clinicians assume that if a drug is "approved" for mania, then it is a mood stabilizer. This is an important and confusing issue, which I address in Chapter 7. I have advocated for identifying mood stabilizer use with prophylactic efficacy. Some would argue that based on this definition, valproate and carbamazepine are not mood stabilizers partly because they do not have FDA indications for maintenance treatment.

My view is that some of the drugs that do not have FDA indications for maintenance treatment (such as valproate and carbamazepine) are mood stabilizers, whereas other drugs that do have FDA maintenance indications (such as olanzapine and aripiprazole) are not mood stabilizers (this should not be surprising; the FDA can make mistakes!). I have explained the latter claim in Chapter 7, but now let's turn to the main valproate maintenance study to defend the former claim.

Two major concepts need to be understood regarding the only placebo-controlled maintenance prophylaxis study of valproate in bipolar disorder (a 1-year randomized comparison with lithium and placebo). First, both lithium and valproate were the same as placebo owing to a high placebo response rate, likely reflecting the exclusion of severely ill patients by researchers owing to ethical concerns about placebo use. Since lithium is proven effective, one cannot conclude, therefore, that the study showed valproate to be ineffective but rather that the study could not have shown that anything was effective, given the nature of the sample. Second, the study used the most difficult design with which to demonstrate efficacy: a nonenriched design. In this approach, patients are allowed into the study as long as they are well (euthymic), no matter what previous medications they might have taken to get well. It is an underappreciated fact that in a secondary analysis limited to those who responded initially to valproate, valproate was more effective than lithium and placebo. This latter design, called *enriched,* in fact became the standard approach in future lamotrigine and antipsychotic trials. In other words, if we compare the studies using the same research design, valproate shows the same efficacy as lamotrigine or antipsychotics. (The reason the FDA did not give an indication for

valproate was that its analysis, which showed efficacy, was not the a priori primary outcome for which the study had been designed.)

All in all, I think that it is reasonable and defensible to conclude that there is some evidence of efficacy for prophylaxis with valproate, especially for depressive episodes in bipolar disorder.

### *Acute Depression*

Many clinicians assume that valproate is not effective in the treatment of acute bipolar depression. There is some clinical lore that valproate may actually be "depressogenic." In fact, three randomized studies show notable benefit with valproate for acute bipolar depression over placebo. Now, these studies are small, and one of them was not statistically significant (but the other two studies were statistically significant, and they all had similar effect sizes favoring valproate). While still limited, this evidence of benefit is much stronger than that for lamotrigine, for example, despite the widespread but false belief that lamotrigine is effective for acute bipolar depression.

Hence, while not definitive, there is some evidence that valproate has acute antidepressant effects. As discussed in Chapter 13, I would expect mood stabilizers to have some antidepressant effects. My view is that valproate has moderate antidepressant effects, which can be sufficient even in monotherapy in some depressed individuals. I would caution that in bipolar disorder type II depression, lower levels of valproate actually may better elicit its antidepressant effects.

### *Special Populations*

Valproate is often preferable to lithium in the elderly owing to lithium's low therapeutic index (see Chapter 14). Lithium may be preferable to valproate in adolescents owing to the latter's increased hepatic risk in younger patients. Nonetheless, with careful monitoring, valproate can be used in children and adolescents. Small studies suggest that valproate can improve substance abuse as well as bipolar disorder in patients with comorbid conditions. Some anxiolytic benefit with valproate also has been recorded. Since valproate is proven effective for migraine, it is an especially useful treatment in patients with bipolar disorder and migraine.



## CARBAMAZEPINE (TEGRETOL)

Carbamazepine's spectrum of efficacy is similar to that of valproate, with the exception that it has perhaps more studies supporting efficacy in prophylaxis and acute bipolar depression. Some long-term studies report less preventive benefit with carbamazepine than with lithium, however. Also, in one randomized, long-term study, carbamazepine also did not reduce mortality from suicide, unlike lithium in the same study. The main limitations to greater use of carbamazepine have to do with its pharmacology and side effects.

### Formulations, Mechanisms, Dosing, and Pharmacokinetics

Carbamazepine is available in generic form, in standard trade formulation (Tegretol), and in two extended-release forms (Tegretol XR or Equetro/Carbatrol). Standard carbamazepine has a half-life of about 6 hours, thus requiring at least twice-daily dosing (unlike valproate and lithium), even with the extended-release formulation. In the outpatient setting, I begin with 200 mg at night and then increase by 200 mg per day every 5 to 7 days until either it is intolerable or therapeutic-range doses are achieved. In the inpatient setting, it is effective to begin with 400 mg at night and increase by 200 mg per day to 400 mg per day every 1 to 2 days. The psychotropic mechanism of action of carbamazepine is unclear. Unlike valproate and lithium, it does not appear to affect many second-messenger systems (such as protein kinase C), but it does affect the second-messenger cAMP. Carbamazepine usually requires doses around 800 mg per day (range 600 to 1,000 mg per day) in twice-daily dosing for an effective serum level of about 8 ng/dL (range 4 to 12 ng/dL). This serum level has been established for acute mania, as well as epilepsy.

### Drug Interactions

Perhaps the most important pharmacologic effect of carbamazepine is its strong induction of the hepatic cytochrome P450 enzyme system. Hence carbamazepine reduces efficacy or blood levels of many other medications. This effect is a major problem in treating patients with other medical conditions, such as the elderly. It is also a major problem in treating bipolar disorder because most such patients are treated with multiple psychotropic medications.

Carbamazepine's 9,10-epoxide metabolite can be neurotoxic (producing delirium or confusion) and may be produced in greater amount in combination treatment with valproate. Consequently, the valproate-carbamazepine combination, though used safely in many patients, should be avoided on a routine basis.

## Side Effects

Carbamazepine has important nuisance side effects as well as serious medical risks (see Table 15.1). Among its associated side effects, which are dose-related, are sedation, double vision (diplopia), ataxia, and dizziness. As an important advantage, carbamazepine does not cause appreciable weight gain in most patients, unlike lithium and valproate.

It is my clinical experience that the most recent slow-release preparation of Carbatrol (which is the same as Equetro) has fewer nuisance side effects than either generic carbamazepine or Tegretol XR. I could be mistaken, and clinicians need to determine this matter for themselves because data are limited. In my practice, however, patients rarely tolerate generic carbamazepine, but they seem to better manage with Carbatrol/Equetro.

## Medical Risks

Carbamazepine, like valproate, is associated with LFT abnormalities. It is also occasionally associated with hepatic failure. It is also associated with rare agranulocytosis (1 in 575,000 cases) and rare Stevens-Johnson syndrome (1 in 10,000 cases). Benign reversible leukopenia also can occur, as can hyponatremia (with associated seizure risk). Nonserious rash is also common.

## Clinical Uses

Carbamazepine is an underappreciated drug. Its lack of weight gain should put it at the fore of mood stabilizer options in groups concerned about weight, such as young women. Since lamotrigine is less effective in the long term for manic episode prevention than for depression, and since it is acutely ineffective for mixed or manic symptoms, carbamazepine would seem to have an important niche in the young woman with predominantly mixed-episode symptoms



or with a history of more severe mania than depression. In such persons, I frequently see lamotrigine used with little benefit, and often carbamazepine is never even tried.

Carbamazepine is most useful in younger individuals who do not have many medical morbidities and are not taking other medications, thus obviating the drug-interaction complications. Further, if a patient with bipolar disorder does not respond well to carbamazepine in monotherapy or in combination with lithium, I tend to avoid continuing combinations with antipsychotics or anticonvulsants owing to the undercutting effect of carbamazepine's hepatic enzyme induction on the blood levels of those other agents. In a study of risperidone added to mood stabilizers, for instance, the combination with carbamazepine was not better than placebo, although the combinations with lithium or valproate were better than placebo. In such settings of polypharmacy, carbamazepine is usually best left out of the mix. (However, paliperidone and ziprasidone do not have drug interactions with carbamazepine, and thus those combinations may be effective).