

Major System Toxicities and Side Effects of Anticonvulsants

Alan C. Swann, M.D.

The use of anticonvulsants is expanding in the treatment of bipolar and related disorders. Although they have characteristics in common, the anticonvulsants currently used are quite diverse and vary in their spectrum of activity, quality of supporting evidence, and organ toxicities. Common side effects of anticonvulsants that can limit tolerability but are not physiologically severe include sedation and other cognitive impairments, tremor, and gastrointestinal side effects. Possibly less common, but of more physiologic significance, are effects on body weight and metabolism and dose-related hepatic and hematologic effects. Severe, but rare, toxicities include skin, bone marrow, and hepatic toxicity due to hypersensitivity. The most important aspect of successful management of severe toxicities is early detection, discontinuation of the medicine, and vigorous treatment of the toxicity. Anticonvulsants can also be associated with fetal toxicity, especially neural tube defects. In general, anticonvulsants are well tolerated and their effectiveness greatly outweighs risk or annoyance from side effects, but side effects must be kept in mind when choosing and monitoring treatment.

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Anticonvulsants have increased the range of options for effective treatment of bipolar disorder. In general, they are well tolerated. Like any pharmacologic treatments, however, they can have acute or long-term toxic effects. These must be taken into account in determining the value of anticonvulsants and developing strategies for their use. This review will focus on major toxicities of the most-used anticonvulsants in treatment of bipolar disorder: carbamazepine, valproate, lamotrigine, gabapentin, and topiramate. I will consider effects of anticonvulsants on the central nervous system, liver, metabolism, and immune system, discuss their use during and directly after pregnancy, and then summarize the relative toxicities of these drugs.

In considering reports of anticonvulsant toxicities, one must consider the populations from which they were derived. Most long-term data are from patients with epilepsy, who may differ from those with bipolar disorder in susceptibility to adverse effects. Second, many of the data from patients with epilepsy are from children. Most patients with bipolar disorder who receive anticonvulsants, at least so far, are adults. Children are more susceptible than adults to many of the metabolic and immune effects of anticonvulsants.

From the Department of Psychiatry, University of Texas Medical School at Houston, Houston.

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Reprint requests to: Alan C. Swann, M.D., Department of Psychiatry, University of Texas Medical School at Houston, 1300 Moursund St., Room 270, Houston, TX 77030 (e-mail: Alan.C.Swann@uth.tmc.edu).

COGNITIVE EFFECTS

Cognitive effects of commonly used anticonvulsants are generally mild. Valproate is associated with mild sedation and a reversible impairment of attention at high doses.¹ Severe sedation is unusual even with 30-mg/kg loading doses.² In a series of 21 patients between 60 and 82 years old, only 2 experienced marked sedation.³ Stoll et al.⁴ reported that a series of patients experiencing cognitive difficulties during lithium treatment improved after their treatment was changed to divalproex sodium.

Among newer anticonvulsants, lamotrigine and gabapentin appear to be associated with mild sedation and minimal or no cognitive performance deficits.⁵ Topiramate, however, is more likely to be associated with deficits in word finding and other aspects of memory and concentration,⁵ which appear dose dependent.⁶

Psychomotor effects of drugs can depend on how they affect mood state. For example, carbamazepine is generally considered to have mildly sedating effects,^{7,8} but Joffe et al.⁹ reported increased motor activity in depressed patients who improved with carbamazepine.

HEPATIC EFFECTS

Most anticonvulsants are metabolized, at least partially, in the liver. Therefore, they or their metabolites have the potential for hepatotoxic effects.

Elevations, usually transient, in liver enzymes are common in drugs that are metabolized in the liver.¹⁰ Severe liver failure is much less common, but has been reported

with carbamazepine,^{11,12} lamotrigine,^{13,14} topiramate,¹⁵ and valproate.^{16,17} Risk is increased by young age, combination therapies, and any coexisting condition that compromises liver function.^{14,16} However, fatalities have also been reported in healthy adults without evidence of previous hepatic or metabolic disease.¹⁷ Fatal liver failure is rare, however, having been reported with valproate in a total of 26 adults in the world literature; 3 were receiving monotherapy.¹⁷

There are 2 principal mechanisms of drug-induced hepatotoxicity. The first is direct toxicity of a drug or metabolite. This toxicity is dose related. An example is toxicity of the valproate metabolite 4-en-valproate, which occurs only when liver immaturity, disease, or excessive load of valproate results in unusual concentrations of this metabolite.

The second mechanism of toxicity is hypersensitivity.¹⁸ This differs from direct toxicity in that hypersensitivity is dose independent, more rare, and associated with fever and eosinophilia and has a shortened latency for development if the drug is readministered. Autoantibodies are occasionally present. I will discuss hypersensitivity to anticonvulsants in more detail in the section on the immune system.

Early symptoms of liver toxicity include apathy, malaise, decreased appetite, nausea, vomiting, and fever. Apathy combined with other signs of more severe febrile illness should alert the clinician to act promptly; patients and their significant others should be alerted to the importance of this combination. Prompt detection of toxicity and discontinuation of treatment are vital for a favorable outcome. Better recognition and early discontinuation of treatment may account for recent increases in recovery rates from drug-induced hepatotoxicity.¹⁶

METABOLIC EFFECTS

Weight gain is the bane of many otherwise valuable psychotropic drugs.¹⁹ Patients may select a less effective treatment if they believe it is less likely to cause weight gain.²⁰ By anticipating problems and combining regulation of activity and diet, however, weight gain can potentially be controlled.¹⁹

Valproate is the anticonvulsant most often associated with weight gain, although others also can have this effect. One study found that, over a 12-month period, 71% of patients taking valproate and 43% of those taking carbamazepine gained weight.²¹ Weight gain with valproic acid occurs most often in patients with low or normal body mass index.²¹ Chronic gabapentin can also be associated with weight gain.^{22,23}

Weight gain during valproate treatment may be, at least partially, independent of change in caloric intake and may be related to impaired β -oxidation of fatty acids.²⁴ Impaired fatty acid intoxication may result from reduced carnitine concentrations.²⁴ Reduction in carnitine levels during valproate treatment is increased if valproate is combined with

drugs that induce microsomal oxidation; accordingly, plasma free carnitine correlates with the valproate level/dose ratio.²⁵ Valproate or a metabolite may compete with carnitine transport.²⁶ This may compound already deficient carnitine in some patients with epilepsy²⁷ and may therefore be less evident in bipolar disorder. Patients with a hereditary defect in carnitine transport may be especially susceptible.²⁸ Healthy adults may be less susceptible to carnitine-related effects because of an adaptive increase over time in renal carnitine reabsorption.²⁹

For the above reasons, carnitine supplementation has been found useful in cases of severe valproate toxicity³⁰⁻³² and in patients, especially children, at high risk.²⁷ Due to the cost of carnitine replacement, and its lack of benefit in low-risk populations, routine carnitine supplementation is not recommended.²⁷

ENDOCRINE EFFECTS

Isojarvi et al.³³ reported obesity, hyperandrogenism, and polycystic ovaries in more than half of a cohort of Finnish women taking valproate for partial complex epilepsy. As noted above, they attributed this effect to weight gain and increased insulin levels and suggested management by switching to an anticonvulsant that caused less weight gain.³⁴ Subsequent studies have cast doubt on the generalizability of any association between polycystic ovaries and valproate. Murialdo et al.³⁵ reported no differences among valproate, phenobarbital, and carbamazepine in polycystic ovaries or hirsutism in a group of women with epilepsy. In bipolar women receiving lithium or valproate, Rasgon et al.³⁶ found no evidence of polycystic ovaries, although menstrual irregularities were common in both treatment groups.

Other endocrine effects of anticonvulsants result from pharmacokinetic interactions. Drugs that induce hepatic microsomal oxidative enzymes reduce concentrations of endogenous compounds, such as dihydroepiandrosterone sulfate, and synthetic estrogens.³⁷

IMMUNE SYSTEM

Diagnosis and management of severe skin rash is considered separately by Hebert and Ralston³⁸ elsewhere in this supplement. I will discuss more general aspects of hypersensitivity to anticonvulsants.

Anticonvulsant hypersensitivity syndrome occurs in about 0.1% of patients treated with certain anticonvulsants, especially aromatic anticonvulsants (phenytoin, phenobarbital, primidone, and carbamazepine), felbamate, and lamotrigine.³⁹ Other drugs with the potential for a similar syndrome include sulfonamides, minocycline, terbinafine, azathioprine, and allopurinol.⁴⁰ A case-control study found the relative risk for Stevens-Johnson syndrome or toxic epidermal necrolysis during the first 8 weeks of anticonvulsant treatment (compared with patients admitted to the same

facility for acute illness or elective procedures) to be 57 for phenobarbital, 91 for phenytoin, 120 for carbamazepine, 25 for lamotrigine, and 24 for valproic acid (data for valproic acid based on 4 cases, all of whom were taking other drugs on this list).⁴¹ Onset is usually delayed by a few days—2 months after the beginning of treatment. Initially, the individual may experience a rash with fever, pharyngitis, and malaise. The initial rash may appear benign. This can be followed by involvement of one or more organ systems, including skin, liver, bone marrow, blood vessels, kidney, and gastrointestinal tract.^{42,43}

Severe hypersensitivity reactions must be differentiated from more benign adverse effects. Benign rash occurs in 5% to 20% of individuals given aromatic anticonvulsants or lamotrigine, for example, whereas Stevens-Johnson syndrome or toxic epidermal necrolysis may occur in only 1 case out of 3000. Hematologic reactions with carbamazepine are similar. About 12% of children and 7% of adults given carbamazepine experience gradual onset of leukopenia during the first 3 months of treatment; this is generally reversible with reduction (or even continuation) of carbamazepine. Patients with white blood cell counts lower than $3.0 \times 10^9/L$ or neutrophil counts below $1.0 \times 10^9/L$ should have dose reduction or discontinuation of carbamazepine and increased monitoring. Routine monitoring is inadequate, however, to detect the rapid development of bone marrow suppression due to hypersensitivity. Patients and physicians must be trained to watch for early clinical signs of anemia, agranulocytosis, or thrombocytopenia.⁴⁴

In general, the mechanism of anticonvulsant hypersensitivity is thought to involve the formation of reactive drug metabolites that irreversibly modify cellular proteins. The modified proteins are believed to elicit an autoimmune response.⁴⁵ Inducers of oxidative metabolism may therefore increase the risk of hypersensitivity. Aromatic anticonvulsants may cross-react (cross-reactivity as high as 70% to 80%³⁹), whereas lamotrigine or felbamate may produce hypersensitivity via distinct modified proteins.⁴⁵

Severe hypersensitivity to anticonvulsants is unusual but develops quickly and unpredictably. Because systematic laboratory monitoring is inadequate, education of the patient and other involved individuals is vital for early detection and management of these reactions.

EFFECTS OF ANTICONVULSANTS DURING PREGNANCY AND THE POSTPARTUM PERIOD

Table 1 provides an overview of the relative risk associated with the different treatments for bipolar disorder, including anticonvulsants, during and after pregnancy.

Developmental Effects

Anticonvulsants have been associated with fetal abnormalities. Neural tube defects have been reported in 1% to 2% of infants who were exposed to anticonvulsants during

Table 1. Treatment of Bipolar Disorder During and After Pregnancy

Relative Risk	Time During Pregnancy		Breastfeeding
	Early	Late	
Relatively safe with rational and careful monitoring	Conventional neuroleptics, electroconvulsive therapy	Most treatments (but see text)	Neuroleptics (low dose), antidepressants, carbamazepine, valproate
Avoid unless necessary	Carbamazepine, valproate, lithium	...	Lithium
Inadequate data	Atypical antipsychotics, lamotrigine, gabapentin, topiramate		

the first trimester.⁴⁶ Other malformations, including facial dysmorphias, skeletal abnormalities, and cardiac defects, are also reported, constituting what is called the fetal anticonvulsant syndrome.⁴⁶⁻⁴⁹ Risk of malformations may be related in part to oxidative metabolites of aromatic anticonvulsants.⁴⁷ Incidence of malformations is increased by concomitant caffeine use; by combination treatments, especially if at least one drug is an inducer of microsomal oxidative enzymes; and by clonazepam if it is combined with other agents.⁵⁰

A recent study of 983 births found a 3.1% incidence of anomalies in infants who were not exposed to any drugs in utero. Anticonvulsants were associated with increased malformation rates: 14.3% with primidone, 11.1% with valproate, 9.1% with phenytoin, and 5.7% with carbamazepine.⁴⁸ Incidence of birth defects in infants exposed to valproate was related to dose and level, showing an increase only when the dose was over 1 g/day and the maternal blood level was at least 70 $\mu\text{g/mL}$.⁴⁸

Limited information is available about long-term outcome in children who were exposed to anticonvulsants. A group of adults who had been exposed to phenytoin or carbamazepine had normal word fluency and lateralization but showed impairments in spatial integrative ability.⁵¹ Children exposed to carbamazepine were found to be smaller than expected.⁵² A group of children who experienced fetal anticonvulsant syndromes had an increased incidence of problems, including learning disabilities, developmental delays, and joint laxity.⁵³

Alternatives to anticonvulsants are also not without problems. In addition to the poorly quantified risk of Ebstein's anomaly, lithium is associated with problems later in and after pregnancy including polyhydramnios, premature labor, neonatal lithium toxicity, and neonatal hypothyroidism.⁵⁴

Postpartum Period

Women with bipolar disorder are at increased risk for recurrence during the postpartum period, so effective treatment is necessary. This raises the question of the presence, and safety, of anticonvulsant medicines in breast milk.

Table 2. System Toxicities of Anticonvulsants

System	Risk Factors	Signs/Symptoms	Level of Risk	
			Relatively High	Relatively Low
Cognitive	...	Concentration, word finding	Topiramate	Lamotrigine
Liver	Combination therapies, enzyme inducers, hepatic compromise, age less than 10 y	Systemic illness with apathy	Carbamazepine, valproate	Gabapentin?
Weight gain	Low/normal weight, women	...	Valproate	Lamotrigine, gabapentin
Immune	Rapid dose increase, previous hypersensitivity, family history, enzyme inducers	Rash with systemic symptoms, then severe skin, hematologic, liver, or other involvement	Carbamazepine, lamotrigine	Valproate
Developing fetus	Combination therapies, enzyme inducers	Neural tube defects, other anomalies	Carbamazepine, valproate	Inadequate data on newer treatments

Table 3. Side Effect Profiles of Anticonvulsants^a

Drug	Cognitive	Liver	Skin	Blood	Weight	Fetus
Valproate	1	2	1	2	3	3
Carbamazepine	1	2	3	3	2	3
Lamotrigine	0	1	3	1	0	?
Gabapentin	2	0	0	0	2	?
Topiramate	3	1	0	0	0	?

^a0 = not a practical concern; 1 = can occur, but not to the extent that this is considered a disadvantage to use of the drug; 2 = generally does not limit use of the drug, but should be monitored especially in susceptible individuals; 3 = requires additional monitoring or may limit use of the drug.

Most studies have found levels of anticonvulsants in milk to be low, so breastfeeding while taking anticonvulsants is considered safe.^{55,56} Information is sparse, however. Blood levels of valproate in infants were reported as 0.9% to 6% of maternal levels, with carbamazepine levels of around 20% of maternal levels.^{57,58}

Little information exists on the adverse effects in breastfed infants whose mothers were taking anticonvulsants. Between 1993 and 1998, there was 1 report of thrombocytopenia in 39 infants whose mothers were taking valproate and 2 cases of hepatic dysfunction in 50 infants whose mothers took carbamazepine.⁵⁶ There is an additional older case report of an infant experiencing hepatotoxicity whose mother received valproate.⁵⁹

Concentrations of lithium in breast milk tend to be somewhat higher, relative to plasma levels, than those of anticonvulsants. There were 2 reports of lithium toxicity out of 11 infants whose mothers were taking lithium.⁵⁶

The general consensus appears to be that pharmacology during breastfeeding is primarily an individual decision based on the maternal history of illness and response to treatment, the possible advantages of breastfeeding to the mother and to the infant, and the possible risks of infant exposure to treatments.⁶⁰ Carbamazepine, valproate, and antidepressants are considered relatively safe^{55,60}; there are almost no data about the newer anticonvulsants. Conventional antipsychotic agents can cause movement disorders in the infant at high doses⁶⁰; risks of newer agents are not known. Lithium is considered less safe due to relatively

high milk/plasma ratios, so if it is used, the rationale for its use should be well documented, and careful monitoring is necessary.⁶⁰

Pregnancy, Childbirth, and Pharmacokinetics

Although relatively few data exist on lamotrigine use during pregnancy, care must be exercised due to its pharmacokinetics in the mother and in the infant.⁶¹ Lamotrigine is transported rapidly across the placenta. During pregnancy, its metabolism appears to be induced, because maternal lamotrigine levels increase rapidly after delivery. Lamotrigine has a high half-life in infants: at 72 hours after childbirth, the plasma level was reported to be 75% that of the cord blood level. Finally, the milk/plasma ratio of lamotrigine is about 0.6. For all of these reasons, lamotrigine should be used only with extreme caution during pregnancy and during the postpartum period in nursing mothers.

Management

Women taking anticonvulsants must be educated about the reproductive effects of these agents and the importance of collaborative planning. This should be discussed thoroughly as early in treatment as possible, and then more specifically if the patient decides that she wants to get pregnant. Because the neural tube is generally closed by the end of the first month, by the time a woman knows that she is pregnant it is too late to prevent anomalies by discontinuing treatment. Folic acid supplementation is a valuable strategy but does not eliminate risk. The decision of whether to continue anticonvulsant treatment during a planned pregnancy depends on the balance between the risk of recurrence of illness and the possibility of risk to the fetus. This balance depends heavily on the patient's priorities and her previous course of illness. If she decides to discontinue previously effective treatment, discontinuation should be gradual (over at least 4 weeks), with the last dose taken at the time of the intended last menstrual period before conception. Treatment alternatives early in pregnancy include conventional antipsychotic drugs, antidepressants such as selective serotonin reuptake inhibi-

tors, and, for severe episodes, electroconvulsive therapy. Later, usual treatment can be reimplemented if desired, with the caveats described in this section.

SUMMARY

Anticonvulsants are playing an expanding role in the treatment of bipolar disorder. These medications are effective for many patients and are well tolerated by most. Like any active treatment, however, they have toxicities that can be substantial. Like the therapeutic effects, toxic effects of anticonvulsants are heterogeneous. Tables 2 and 3 summarize the severity of major side effects and toxicities among anticonvulsants. Strategies for optimal use of anticonvulsants are still evolving. Their specific roles will require a balance between toxicity, subjective tolerability, and effectiveness.

Drug names: azathioprine (Imuran), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), felbatol (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), minocycline (Minocin and others), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), primidone (Mysoline), terbinafine (Lamisil), topiramate (Topamax), valproic acid (Depakene).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine, clonazepam, gabapentin, lamotrigine, and topiramate are not approved by the U.S. Food and Drug Administration for treatment of bipolar disorder.

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