# Mood Stabilizers and Anticonvulsants

## GENERAL PRESCRIBING TIPS

In this chapter, we focus on the non-antipsychotic mood stabilizers—meaning lithium, valproic acid, lamotrigine, carbamazepine, and oxcarbazepine. The antipsychotics, most of which are effective for bipolar disorder, are covered in their own chapter. This chapter also includes anticonvulsants that may not be particularly useful in treating bipolar but may be used from time to time in psychiatric practice.

Here are some general observations:

- *Manic episodes.* Generally the most effective drugs for rapid control of acute mania are antipsychotics and mood stabilizers, often combined with benzodiazepines. While head-to-head studies are scant, clinical lore has it that olanzapine, quetiapine, and haloperidol are the most rapidly effective antipsychotics in highly agitated and psychotic patients. Unfortunately, all three medications are highly likely to cause side effects.
- *Bipolar depression.* The medications with FDA indications for the treatment of bipolar depression include the combination of fluoxetine and olanzapine (Symbyax), quetiapine (Seroquel), lurasidone (Latuda), and most recently cariprazine (Vraylar) and lumateperone (Caplyta). Most have drawbacks, related to side effects (Symbyax and Seroquel) or cost (Vraylar and Caplyta). There's good evidence for lithium, lamotrigine, and aripiprazole for bipolar depression, and you can add bupropion to any mood stabilizer—bupropion being the antidepressant least likely to cause a manic switch.
- *Maintenance treatment of bipolar disorder.* Maintenance treatment should include a mood stabilizer with a proven record of reducing cycling and increasing the time period between acute episodes. Only a few meds have such a record. These include lithium (more effective at preventing mania than depression), lamotrigine (more effective at preventing depression than mania), and some second-generation antipsychotics (olanzapine, aripiprazole, quetiapine, and ziprasidone, all more effective at preventing mania than depression). In addition, valproic acid and carbamazepine are commonly used as maintenance treatment.

### Class Warnings

Several mood stabilizers are also classified as anticonvulsants, and you should note that the FDA issued a black box warning regarding suicide for anticonvulsants as a class. The warning is based on pooled analysis of 199 trials involving various antiepileptics (regardless of indication) that showed an increased risk of suicidal thoughts/behavior (incidence rate: 0.43% of treated patients compared to 0.24% of patients receiving placebo). The risk was observed as early as one week after initiation and continued through duration of trials (most of which were ≤24 weeks). The risk was higher for patients with seizure disorders compared to those receiving anticonvulsants for other indications.

Another class warning for the anticonvulsants regards a potentially serious, sometimes fatal multi-organ hypersensitivity reaction syndrome (drug rash with eosinophilia and systemic symptoms, or DRESS), which has rarely been reported with some antiepileptic drugs. Symptoms may include fever, rash, and/or lymphadenopathy; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems. Early symptoms of hypersensitivity reaction (eg, lymphadenopathy, fever) may occur without rash. If this occurs, discontinuation and conversion to alternate therapy may be required.

### Switching or Discontinuing Mood Stabilizers

Patients with bipolar disorder are at relatively high risk for relapsing to either manic or depressive episodes. For this reason, switching or discontinuing mood stabilizers requires special caution. For instance, patients who discontinue maintenance lithium have a 60%–90% risk of recurrence of a mood episode within a year. And this risk is greater the more abruptly the lithium is stopped: Discontinuing lithium over two to four weeks is significantly less likely to lead to relapse than discontinuing in two weeks or less (Baldessarini RJ et al, *Am J Psychiatry* 1997;154(4):551).

While we don't have as much data on how to discontinue mood stabilizers other than lithium, it's reasonable to assume that relapse risks are higher with more rapid tapering. When switching among lithium, valproate, carbamazepine, or lamotrigine, you should cross-taper as gradually as is feasible—typically over at least a two-week period.

Here's an example of how you might take two weeks to gradually transition a patient from lithium 1500 mg daily to a therapeutic dose of valproate:

- Days one to three: Continue lithium at 1500 mg daily as you start valproate at 250–500 mg QHS.

- Days four to six: Decrease lithium to 1200 mg daily. Increase valproate to 750–1000 mg QHS.
- Days seven to nine: Decrease lithium to 900 mg daily. Increase valproate to 1000–1250 mg daily QHS or in divided doses.
- Days 10–12: Decrease lithium to 600 mg daily. Increase valproate or hold depending on side effects/blood level.
- Days 13–15: Decrease lithium to 300 mg daily. Maintain valproate dose.
- Day 16: Discontinue lithium. Maintain valproate dose.

This guideline is applicable to most switches, with the exception of switching from any mood stabilizer to lamotrigine, which requires a very slow dosing schedule to lower the risk of a serious rash. In switching to lamotrigine, you will typically maintain the first mood stabilizer at a nearly full therapeutic dose while titrating lamotrigine in small increments (see lamotrigine fact sheet for details) up to 100 mg daily, which requires about four weeks. You can then start tapering the first medication as you continue to increase lamotrigine. In the special case of switching from valproate to lamotrigine, you must slow down the titration even more.

### Anticonvulsants

There's a great tradition in psychiatry of adopting antiepileptic drugs for use in psychiatric syndromes. In some cases, as above, this strategy has yielded effective treatments. But for gabapentin, pregabalin, and topiramate, the payoff has been fairly scant. All three were initially touted as having efficacy in bipolar disorder, based on uncontrolled trials. However, subsequent data from randomized controlled trials did not support this indication.

Nonetheless, these drugs have found their places in other spheres, especially disorders related to anxiety or substance use. For example, pregabalin is approved for generalized anxiety disorder in parts of Europe. It also has pretty convincing data for effectiveness in helping patients discontinue benzodiazepines. Topiramate seems to have a niche for patients with alcohol dependence and for any patient who wants to lose weight. Gabapentin is a non-addictive alternative to benzodiazepines for anxiety and alcohol dependence.

### Side Effects

The newer anticonvulsants are appealing because they are generally less toxic than the older agents, do not require serum level monitoring, and in most cases have a lower risk of drug interactions. However, the antiepileptics have a class warning for increased risk of suicidal thoughts and behavior; this warning stems from pooled analysis of trials (for seizure disorders as well as other indications) that showed a nearly doubled incidence of suicidal thought and behavior (0.43% for anticonvulsants vs 0.24% for placebo).

You'll note that the DEA has deemed pregabalin a controlled substance (Schedule V). Some states are reclassifying gabapentin as a controlled substance or mandating reporting to prescription drug monitoring programs (PDMPs). Reports of diversion and misuse of both pregabalin and gabapentin have been accumulating. Recreational use seems to be higher among individuals with opioid use disorder, and this may be related to the potentiation of euphoria described when the two are used together. Similar to combining benzos with opioids, the combination of gabapentinoids and opioids also increases the risk of opioid-related death. When using these in patients, be sure to monitor for misuse or diversion.