Bipolar disorder (BD) is a recurrent, life-long psychiatric illness affecting nearly 2% of the world population\(^1,2\) that is characterized by episodes of mania and depression interspersed among periods of relative mood stability.\(^3\) The illness causes an enormous health burden, which makes understanding its pathophysiology and treatment patterns a substantial priority.\(^4\) In the 1950s, lithium was found to be effective for treating acute manic episodes and preventing relapse in BD.\(^5\) Since then, valproate and carbamazepine also have been FDA-approved for treating mania.\(^6,7\) Antipsychotics have also shown evidence of efficacy in BD treatment,\(^8,9\) particularly for use in acute settings for more rapid effect or for a limited duration,\(^10\) which has led some to refer to them as “mood stabilizers.”\(^11\)

In this article, we describe changes in trends of prescribing medications to treat BD, the role of ion dysregulation in the disorder, and how a better understanding of this dysregulation might impact the choice of treatment.

Changes in pharmacotherapy for bipolar disorder

From 1997 through 2016, the use of lithium for BD decreased from >30% of patients to 17.6% (with a nadir of 13.9% from 2009 to 2012).\(^12\) Over the same period, the use of nonlithium mood stabilizers decreased from 30.4% to approximately 4.8%, while second-generation antipsychotic (SGAs) use increased from 12.4% to 50.4%.\(^12\) Distressingly, antidepressant use increased from approximately 47% to 56.8%, and antidepressant use without concomitant mood stabilizers increased from 38% to 40.8%, although the rate of antidepressants without either a mood stabilizer or an antipsychotic remained relatively stable (14.9% to 16.8%).\(^12\) In randomized trials, when added to mood stabilizers, antidepressants have consistently failed to separate from placebo,\(^13-15\) but they can destabilize the illness, resulting in increases in mania, depression, and subsyndromal mixed symptoms.\(^16-18\)

It is easy to understand clinicians’ attempts to address their patients’ distress due to depressive symptoms that do not resolve with mood stabilizers.\(^19,20\) Similarly, the increased use of antipsychotics is driven by evidence that antipsychotics are effective for treating bipolar depression and preventing the recurrence of manic and (for some antipsychotics) depressive episodes.\(^21,22\) However, long-term antipsychotic use causes brain volume change in patients with schizophrenia\(^23\) or major depressive disorder\(^24\) and in nonhuman primates\(^25,26\); metabolic
abnormalities; and cardiovascular adverse effects. Antipsychotics are believed to be associated with withdrawal psychosis. In the head-to-head Clinical Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE) study, quetiapine was as effective as lithium but associated with more adverse effects. Importantly, the estimated disability-adjusted life years of patients with BD increased by 54.4% from 6.02 million in 1990 to 9.29 million in 2017, which is greater than the increase in the incidence of BD (47.74%) over the same time. This means that despite the dramatic increase in treatment options for people with BD, functional outcomes have declined.

One major difference between antipsychotics and mood stabilizers is that antipsychotics do not alter the underlying abnormal pathology of BD. An ideal pharmacologic intervention is one that corrects a known pathophysiologic anomaly of the condition being treated. There are no demonstrated abnormalities in the dopamine or serotonin systems in individuals with BD, but long-term use of antipsychotics may create dopaminergic alterations. One of the most reproducible biomarkers associated with manic and bipolar depressed mood states is increased intracellular sodium and reduced ability to correct a sodium challenge. By normalizing intracellular sodium levels, lithium and the mood-stabilizing anticonvulsants uniquely and specifically counter known physiologic abnormalities in patients with BD.

The role of ion dysregulation

The pathophysiology of BD remains elusive. A multitude of lines of evidence link BD to abnormal neuroimaging findings, oxidative stress, inflammation, and mitochondrial disease, but there is still no unifying understanding of these findings. Ion dysregulation appears to be central to understanding and treating BD.

Despite extensive genetic studies, no genes have been identified that mediate >5% of the risk for BD. Nonetheless, 74% of all genes identified as mediating risk for BD code for proteins essential for the regulation of ion transport and membrane potential. The 2 genes that contribute the greatest risk are CACNA1C and ANK3, which code for a calcium channel and a cytoskeletal protein, respectively. ANK3 codes for ankyrin G, which plays a role in proper coupling of the voltage-gated sodium channels to the cytoskeleton. An additional risk gene, TRANK1, contains multiple ankyrin-like repeat domains, which suggests some shared functions with ANK3. More importantly, the most reproducible pathophysiologic findings in BD are dysregulation of sodium, potassium, hydrogen, and calcium transport, with consequent alteration of depolarization potential, neuronal excitability, and calcium-mediated processes. For example, increased sodium and calcium within cells have been observed in both mania and bipolar depression, and these levels normalize during euthymia. All medications that are effective for treating BD may reduce intracellular sodium or calcium; traditional mood stabilizers do so directly by inhibiting voltage-sensitive sodium channels in an activity-dependent manner or displacing intracellular sodium, whereas antipsychotics do so indirectly by increasing sodium pump activity through inhibition of second messengers of the dopamine D2 family of receptors.

The extent of ion dysregulation is directly associated with the expressed mood state of the illness. A small reduction in the activity of the sodium pump results in a small increase in intracellular sodium (approximately 10 mM). This led to the hypothesis that increased intracellular sodium causes the transmembrane potential to increase closer to membrane depolarization threshold, which increases excitability of affected neurons. Neurons are likely to fire and propagate signals more easily, which may manifest as symptoms of mania, such as increased energy, activity, lability, excitability, irritability, tangentiality, and looseness of associations. As the process of increased intracellular sodium progresses, a minority of neurons are expected to have...
their transmembrane potentials depolarize sufficiently for the resting membrane potential to go beyond threshold potential. Such neurons are in a state of constant depolarization (also known as depolarization block), which disrupts neuronal circuits. The difficulty in progression of these signals results in the classic bipolar depression symptoms of low energy, reduced activity, and slowing of all brain activity that is seen as psychomotor slowing.

**Implications for treatment**

Medications for treating bipolar illness include lithium, anticonvulsants, benzodiazepines, first-generation antipsychotics, and SGAs. Mood stabilizers (lithium and certain anticonvulsants) correct the previously mentioned sodium abnormality by reducing sodium entry into the cell in an activity-dependent manner. As the only agents that directly address a known pathophysiologic abnormality, they are foundational in the treatment of BD. Lithium effectively treats acute mania and prevents relapse. It preferentially targets the active neurons, entering through both voltage-responsive and neurotransmitter-coupled channels. This results in an increase of intracellular lithium concentrations to as much as 8 times that of the extracellular concentration. These ions displace intracellular sodium ions in a 1:1 ratio, which results in a reduced intracellular sodium concentration that reduces the excitability of neurons.

Substantial evidence supports the use of valproic acid for initial and maintenance treatment of BD. It inhibits the voltage-sensitive sodium channel when the channel is open, which results in an activity-dependent action that selectively impacts rapidly firing neurons. The voltage-gated sodium channels exist nearly exclusively on the axon, beyond the hillock; as such, valproic acid will only inhibit neurons that fire, whereas lithium accumulates throughout the neuron and will affect depolarization in the neuronal soma as well as the firing in the axon. Additionally, valproic acid has been observed to enhance gamma-aminobutyric acid (GABA) levels and transmission. A meta-analysis that included 6 randomized controlled trials illustrated that, acutely, valproate was not different from lithium’s overall efficacy (RR 1.02; 95% CI, 0.87 to 1.20), but was associated with reduced dropout rates compared with placebo or lithium (RR 0.82; 95% CI, 0.71 to 0.95 and RR 0.87; 95% CI, 0.77 to 0.98, respectively).

Lamotrigine is an anticonvulsant used for initial and maintenance treatment of BD, with greater efficacy for depressive episodes; it also has notable effect for treating bipolar depression, although it is not FDA-approved for this indication. Lamotrigine inhibits sodium influx by binding to open voltage-gated sodium channels but also appears to reduce N-methyl-D-aspartate–mediated sodium entry, thereby acting both prehillock and posthillock.

Carbamazepine is an anticonvulsant FDA-approved for treating BD. Like valproate, it acts by inhibiting voltage-gated sodium channels in an activity-dependent manner, which means it preferentially inhibits the most active neurons and those with higher intracellular sodium.

Benzodiazepines, which have shown to be effective for treating acute mania, potentiate synaptic GABA receptors accruing an elevation in intracellular chloride influx. Despite acute efficacy, benzodiazepine use is limited because these agents are associated with worsening long-term, substance use–related outcomes.

Antipsychotics are effective for treating mood disorders and their use has been rising dramatically. The antiminic effect of all antipsychotics is believed to be mediated through dopamine D2 blockade, since use of a dose sufficient to block D2 receptors is required, and haloperidol, which acts exclusively on the D2 receptor, is equal to SGAs in its antiminic effect. Blockade of the D2 receptor will increase the activity of the sodium pump (sodium and potassium-activated adenosine triphosphatase) thus reducing intracellular sodium and calcium concentrations. When antipsychotics are used as antidepressants,
they are generally used at doses lower than those used to treat mania.78 Antipsychotics are effective for treating BD, and may work more quickly than other agents for treating acute mania.79 However, maintenance or prevention trials tend to favor mood stabilizers.35,60,80 Several add-on studies have found the combination of a mood stabilizer plus an antipsychotic is superior to a mood stabilizer alone or an antipsychotic alone.81

An argument for mood stabilizers
Evidence suggests mood stabilizers and other approaches, such as antipsychotics, are almost equivalent for treating acute mania, with a small clinical advantage of mood stabilizers for preventing relapse. In general, current treatment guidelines do not distinguish mood stabilizers from antipsychotics as the first-line treatment.82 Over the past 20 years, antipsychotic use has increased while mood stabilizer use has decreased, so that presently a patient with BD is more likely to be prescribed an antipsychotic than a mood stabilizer.83 Over the same time, dysfunction among patients with BD has increased.33 Antipsychotics are appealing because they appear to be equally effective and generally well tolerated. But these agents cause problems that are difficult to see in routine visits, such as metabolic27-31 and cardiovascular adverse effects29 as well as reductions in brain volume.23-26 Mechanistic research suggests that mood stabilizers directly correct known pathophysiologic anomalies with additional protective effects, whereas antipsychotics appear to create new abnormalities and contribute to medical problems. Clinicians need to look beyond the similarities in acute efficacy and make a more broadly supported, evidence-based choice for managing BD, which clearly places mood stabilizers as the first-line agent and antipsychotics as reasonable alternatives. At a minimum, mood stabilizers should be viewed as the foundation to which antipsychotics can be added.

References
7. Weisler RH, Keck PE Jr, Swann AC, et al. Extended-release carbamazepine capsules as monotherapy for acute mania in...
34. Sleem A, El-Mallakh RS. Adaptive changes to antipsychotics: their consequences and how to avoid them. Curr Psychiatry. 2022;21(7):46-50,52. doi:10.12788/cp.0p062


Clinical Point
Mood stabilizers should be viewed as the foundation to which antipsychotics can be added.