Bipolar disorder

Drug candidates specifically targeting the disease may offer hope in the long term.

BY LINDA RICHARDS

It's a disease that takes the lives of one of every seven patients through suicide. The World Health Organization ranks it sixth among leading causes of disability. Despite these statistics, pharmaceutical companies have focused little on bipolar disorder medications.

"There's not a lot in the pipeline," admits Todd Gould, research fellow at the National Institute of Mental Health's (NIMH's) Laboratory of Molecular Pathophysiology. "There has been little progress in developing truly novel drugs specifically for the treatment of bipolar disorder. Almost without exception, all of the new agents are simply central nervous system-penetrant drugs that have been developed for other disorders, most notably epilepsy and schizophrenia."

However, another chapter may be unfolding for bipolar disorder, a mental illness characterized by periods of both prolonged and profound depression and excessively elevated mood known as mania. A flurry of studies into the disorder's pathophysiology and a strong interest in its genetic causes bode well for a number of novel treatment agents.

Treating bipolar disorder presents numerous challenges. Its symptoms vary widely among people, making treatment and diagnosis difficult. "It's an incredibly difficult illness to treat," says Sara Corya, who worked for years as a psychiatrist and is now a medical adviser on Eli Lilly's Zyprexa product team. "There's such a variation in how a patient looks on any given day."

According to the Depression and Bipolar Support Alliance, it takes a person 10 years and an average of four doctors to get properly diagnosed. Even so, treatment guidelines for continuing disease management are wanting. Long-term placebo-controlled studies are lacking because of ethical and practical issues. About half of patients stop taking medication, most because they fear side effects or deny their illness. Even for those who do take their medications, many respond poorly over time and often relapse.

PHOTODISC

The history of bipolar disorder is important to understanding the disease, says Samuel Gershon, president of the International Society for Bipolar Disorders. Before 1949, the typical treatment was electroshock treatment, hospitalization, and powerful sedatives, such as barbiturates and morphine. Then two medications were discovered, both by chance.

Encouraged by guinea pig experiments, in 1949 Australian psychiatrist John Cade administered lithium to 10 patients and discovered their symptoms decreased dramatically. "Still, lithium was essentially ignored until the early 1970s, when it was finally FDA-approved in the United States," Gershon says.

The second breakthrough was chlorpromazine (Thorazine), an anesthetic that in 1952 Parisian physicians noticed had a quieting effect on manics and schizophrenics. Thorazine soon became a mainstay for psychiatric cases and helped empty out many state institutions. The drug, Gershon points out, "did reduce hallucinations and delusions, and controlled behavior, making patients much more manageable." Over time, however, severe neurological side effects became common.

In the 1960s, two anticonvulsants—carbamazepine (Tegretol) and valproic acid—were found to be useful in mood disorders. A newer generation of drugs emerged in the 1980s, notably Abbott Laboratories' Depakote, an improved anticonvulsant, and clozapine (Clozaril), the first antipsychotic drug with fewer side effects.

"Depakote and the newer psychotics are all refinements and synthetic copies of Thorazine and Tegretol," Gershon explains. However, while these medications show some efficacy in bipolar disorder, they are hand-me-downs developed for treating epilepsy or schizophrenia.

Pathophysiology

Researchers have made big strides in understanding the pathophysiology of bipolar disorder, and more targeted drugs are expected to emerge. In recent years, neuroimaging and postmortem analysis have shown reductions in the density and/or sizes of neurons and supporting glial cells in the neocortex, the part of the brain associated with higher levels of processing information. Some areas of the brain, such as the emotion-generating amygdala, show excessive activity.

Some researchers theorize that individuals susceptible to bipolar disorder suffer an increasing number of minor neuronal insults that result in abnormal programmed cell

death, or apoptosis, and which over time lead to episodes of mania or depression. Sufficient brain damage may ultimately cause mood episodes to recur with few environmental or behavioral stressors.

In the mid-1990s, mood disorder theories were based on "first-messenger" neurotransmitters that work between neurons, with treatment aimed at increasing serotonin and norepinephrine levels. While this helped improve some antidepressants, it had limited utility in treatments for bipolar mania. Interest then shifted to second-messenger systems that rely on intracellular enzymes to relay information, a slow process utilizing an intracellular signaling cascade, which explains why current drugs often take weeks to months to exert their full effect.

At the same time, researchers have learned how the current mood stabilizers and antidepressants stimulate pathways for cell survival and increase factors that improve cellular resiliency, thereby increasing the communication between neurons.

"Emerging evidence implicates changes in cellular resiliency, neuroplasticity, and additional cellular pathways in the pathophysiology of mood disorders," Gould says. "The new understanding ushers in the search for novel targets, perhaps to bring about normal plasticity or for the lessening of hyperactive processes, which may be associated with the changes we are observing with neuroimaging or postmortem techniques."

Many others are pinning their hopes on genetics, where Gould expects major changes in the next 10 to 20 years. "Bipolar disorder is a complex disorder with many causes—disease heterogeneity—and multiple genes that lead to susceptibility—genetic heterogeneity," he explains. Genes have been identified but lack replication studies. A gene discovery timeline similar to that seen for schizophrenia is expected, where 5 to 10 susceptibility genes were confirmed over 5 years.

Current therapies

Bipolar disorder is no longer considered an episodic illness with full recovery between episodes; rather, most bipolar patients have lingering residual symptoms. Consequently, treatment has shifted toward dealing long-term with the entire illness rather than just with episodes. "The most important need is bipolar maintenance," Gershon says, controlling the ups and downs and restoring function.

Most bipolar patients take an average of three medications. In addition to a mood stabilizer such as lithium or valproate, an antipsychotic is sometimes prescribed for its antimanic effects, and/or antidepressants for those experiencing acute depressive episodes. Although lithium has become a lifesaver for many, several studies have shown that 20 to 40% of patients fail to show a full or adequate response. Other classes of drugs used include anticonvulsants, antianxiety agents, hypnotics, and, occasionally, calcium channel blockers.

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The FDA approved the anticonvulsant lamotrigine, marketed by GlaxoSmithKline as Lamictal, in 2003 for bipolar maintenance, and the drug is often recommended for depression or rapid cycling between depression and mania. There is some evidence that patients on Lamictal do not switch into, or to the same level of, mania as with other drugs, Gershon says. Studies also show it's effective in about two-thirds of patients who have not responded to lithium or other mood stabilizers.

Several drugs have been added recently to the bipolar disorder arsenal, including two approved in January. Lilly's Symbyax, a combination of the antipsychotic olanzapine (Zyprexa) and the antidepressant fluoxetine (Prozac), became the first medication approved for bipolar depression. Studies show that Symbyax dramatically increases all three neurotransmitters: dopamine, norepinephrine, and serotonin.

Moreover, while Lilly makes no claim, the onset of action for depression appears quicker with Symbyax than with Prozac alone. "Something is happening at a molecular level in a synergistic way," Lilly's Corya says. "There's a synchronized chemical reaction in the brain, a very robust response that happens quickly and is a sustained response."

Studies of Symbyax have only lasted eight weeks, so it's unclear how long the drug

Bipolar disorder at a glance

Definition	Also known as manic depression, a person's mood alternates between the poles of mania and depression, with moods lasting hours, weeks, or months.
Prevalence	Estimated 14.1 million people worldwide, with different disease types depending on the patterns and severity of symptoms.
Symptoms	Varying symptoms of mania and depression, with mild to severe swings between episodes of each that disrupt normal life activities; typically develops in late adolescence or early adulthood.
Cause	Most scientists agree there is no single cause but rather many factors, both genetic and environmental, acting together to produce the illness.
Detection	It cannot yet be identified physiologically, as through a blood test or a brain scan. Diagnosis is based on symptoms, course of illness, and family history.
Treatment	Stabilization of mood swings through long-term medication and psychosocial intervention.
Costs	Estimated $24 billion per year in the United States, with the average cost per case ranging from about $11,000 for a single manic episode to $625,000 for a person with nonresponsive episodes.

Source: National Institute of Mental Health; International Society for Bipolar Disorders.

should be taken. It's also unknown whether Symbyax will produce a switch into mania over time. "Prozac is a perfectly good antidepressant and olanzapine an effective acute antipsychotic," Gershon says. "But we still need definitive evidence that it will prevent a switch into mania."

Two schizophrenia medications, Janssen's risperidone (Risperdal) and AstraZeneca's quetiapine (Seroquel), received FDA approval for bipolar indications in December 2003 and January 2004, respectively. Both are indicated for single therapy or in combination with lithium or valproate for short-term treatment of acute mania associated with bipolar I, the most severe form of the disorder. Risperdal is also indicated for mixed episodes, in which depression and mania coexist. Perceived and marketed as very safe, Risperdal and Seroquel have been gaining market share over Zyprexa. Despite some advances, however, these atypical antipsychotics still carry an increased risk of diabetes, weight gain, and high cholesterol. In August, the FDA approved Pfizer's atypical antipsychotic Geodon (ziprasidone HCl-ell) for treating acute bipolar mania, including manic and mixed episodes.

Pipeline drugs

Lilly and Shire Pharmaceuticals are seeking broader indications for two already approved drugs—Zyprexa for bipolar maintenance and the epilepsy drug carbamazepine (Carbatrol) for bipolar disorder. But aside from these Phase III trials, the pipeline for bipolar disorder drugs is thin.

However, several candidates do offer exciting long-term potential therapeutic targets for lithium's actions. Knowing that lithium inhibits the functions of several enzymes, Gould and his NIMH colleagues are looking at glycogen synthase kinase (GSK), specifically brain-penetrant GSK-3 inhibitors, as novel drug candidates that will work like lithium but with reduced side effects.

"There is a huge interest by pharmaceutical companies to develop a potent GSK-3 inhibitor," Gould says, primarily because of the potential for use in also treating diabetes and Alzheimer's. "It would not be a stretch to say that every pharmaceutical company has a GSK-3." The first clinical trials for brain-penetrant GSK-3s are scheduled for Alzheimer's.

Inhibitors of IMPase (inositol monophosphatase), which Merck has studied for at least 10 years, are still at the preclinical stage. "What lithium is hypothesized to do is inhibit IMPase, which decreases inositol concentrations. This results in reduced phosphatidylinositol synthesis and, as a result, this second-messenger system grinds to a halt," explains John Atack, research scientist at Merck. While IMPase inhibition works in the test tube, it hasn't proven clinically feasible—yet. "It's a catch-22," he says. "In order to inhibit the enzyme we need charged groups, and those charged groups don't allow the compound to cross the cell membrane or the blood–brain barrier."

There's also a growing body of data suggesting that agents that modulate a major neurotransmitter system, called the glutamatergic system, may be very helpful. After exciting results in neurodegenerative diseases, these agents are being tested in "proof-of-concept" studies in mood disorder patients. One glutamate release inhibitor is riluzole, a neuroprotective agent with anticonvulsant properties currently approved in the United States, Europe, and Japan for treating amyotrophic lateral sclerosis. Recent case reports and an open-label clinical trial support riluzole's efficacy in treatment-resistant depression.

GlaxoSmithKline's Lamictal also has glutamate release inhibitor properties, and some smaller biotechnology companies are involved in GSK-3 related research as well. However, with most current drugs used for bipolar disorder coming off the existing central nervous system and mental health markets—where combined sales of antidepressants, antipsychotics, and anti-epileptics exceed $40 billion per year—the field continues to be dominated by major pharmaceutical companies.

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