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No New Meds

With drug firms in retreat, the pipeline for new psychiatric medications dries up

By Laura Sanders

Web edition: February 7, 2013
Print edition: February 23, 2013; Vol.183 #4 (p. 26)

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Psychiatry seemed poised on the edge of a breakthrough. In early 2011, after decades of no radically new drugs, a fundamentally different schizophrenia treatment promised relief from the psychotic hallucinations and delusions plaguing people with the disease. The new compound, devised by chemists at Eli Lilly and Co., hit a target in the brain that older medicines had ignored.

All signs pointed to success. In mice, a similar molecule could block the schizophrenia-like effects of PCP. In people the new drug, LY2140023, appeared to curb psychotic behavior with few side effects, small pilot studies showed. In March 2011, Lilly began enrolling 1,100 people in a definitive Phase III clinical trial, the final test designed to show conclusively that the new compound worked.

A year and a half later, the drug was dead. After years of work and millions of dollars of investment, the failure was crushing. People with schizophrenia were no better on the new drug than similar people taking a placebo, early results indicated. "I'm disappointed in what these results mean for patients with schizophrenia who still are searching for options to treat this terrible illness," Jan Lundberg, president of Lilly Research Laboratories, said in a press release.

Although the results were devastating, many in the field weren't surprised. For new drugs designed to treat complex brain disorders such as schizophrenia, depression and anxiety, the odds of success are exceedingly slim. Given the current state of affairs in the drug discovery world, some would argue those odds are close to zero. Not a single drug designed to treat a psychiatric illness in a novel way has reached patients in more than 30 years, argues psychiatrist Christian Fibiger of the University of British Columbia in Kelowna, who described the problem in a 2012 *Schizophrenia Bulletin* editorial. "For me, the data are in," says Fibiger, who has developed drugs at several major pharmaceutical companies. "We've got to change. This isn't working."

Fibiger is not alone in thinking the existing approach needs a radical overhaul. Psychiatrists and neuroscientists around the world recently have begun sounding the alarm that the field is in crisis. Drug development for complex psychiatric illnesses is misguided, they argue, stuck churning out slight variations on therapeutic themes that didn't work all that well to begin with. Faulty assumptions, animal models that don't look anything like human diseases, hazy diagnoses and a lack of knowledge about how the brain works have all thwarted the search for better drugs.

Of course, fixing a brain poses challenges that don't apply to other body parts, says neuroscientist Steven Hyman of the Broad Institute of MIT and Harvard. "You can't just open up the hood, take out a chunk and see what's happening," he says. And even if that were possible, it probably wouldn't add much clarity, Hyman argues in the October 10 *Science Translational Medicine*. "Brain research is really hard," says Hyman. "No one should be blamed for how hard this is. But we did get stuck."

Pharmaceutical exodus

At a meeting of the American College of Neuropsychopharmacology late last year, this crisis was the predominant theme. "It's become a topic with a lot of talk and no idea of where to go," Hyman says.

Drug discovery is a tough, slow business. Initial exploratory work to identify a

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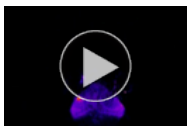

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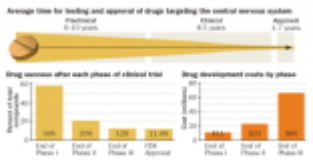
most serious symptoms of schizophrenia. On top of that, many of these medicines have side effects so objectionable that people stop taking them.

Despite a dire need for better treatments and a large market — one in four Americans suffers from a diagnosable mental illness in any given year — many drug companies are retreating. Though some small, targeted efforts remain in place, pharmaceutical giants GlaxoSmithKline, AstraZeneca and Novartis recently shuttered their main brain drug discovery programs. "It's pretty scary when you get down to it," says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development.



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BROKEN PIPELINE

View larger image | For compounds that affect the brain, the chance of failure is high at every step in the testing and approval process (overall success through clinical testing shown above). Generally, these drugs cost more to develop and take longer to reach patients than other drugs. Source: Tufts Center for the Study of Drug Development; S. Egts

This exodus makes sense: Companies can't afford to spend so much time and money only to have a drug fail in Phase III trials, as LY2140023 did.

A survey of pharmaceutical and biotechnology companies revealed the perils of investing in drugs that target the brain. These drugs are more likely to fail and leak out of the pipeline than other kinds of medications. And brain-targeting drugs spend an average of 8.5 years in human tests alone, more than two years longer than the average for other kinds of drugs. "These tend to be very difficult, expensive clinical trials," Kaitin says. Companies that endure a late-stage failure of a drug after years of testing take a huge financial hit. "Very few companies can withstand that," he says.

Drug firms are also feeling the squeeze from generics, cheaper versions of a drug that can be sold after a certain length of time by companies that didn't have to pay for the original development and testing. To stay profitable, developers need to come up with a fundamentally new drug. "It's really a breakthrough or nothing," Kaitin says. "And breakthroughs are hard to come by."

Some researchers point to reasons for hope. Biomedical advances such as genetic sequencing and brain-scanning technology may usher in a deeper understanding of these complex disorders. Many experts, though, argue that for these discoveries to translate into help for patients, things have to change.

Playing it safe

Most psychiatric drugs in use today originated in serendipitous discoveries made many decades ago. In 1952, doctors noted that patients on the antituberculosis drug iproniazid became euphoric. The observation launched iproniazid, the first antidepressant. A version of the schizophrenia drug chlorpromazine was originally tested in the 1950s as an anesthetic. Around that time, a French surgeon recognized the drug's potential in psychiatry, noting that before surgery patients on the drug became "calm, somewhat somnolent, and relaxed."

Since then, most new psychiatric drugs have been subtle variations on these and a handful of other original molecules. "You get lucky by finding a medicine that helps," Insel says. "Then you create another medicine that looks slightly different."

MORE

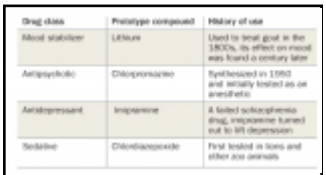
though the technology got better and better, frankly, our success rate got worse and worse," Fibiger says.

After the discoveries of chlorpromazine and another antipsychotic drug, haloperidol, in the 1950s, scientists figured out that these drugs changed the brain's levels of the chemical messenger dopamine. Since then, the relationship between dopamine and schizophrenia has been hotly pursued by the research community, even though it is not exactly clear how those drugs work to combat symptoms. Thousands of studies have been published describing the link between dopamine and schizophrenia. In turn, all of the current drugs for schizophrenia target the brain's dopamine system. (LY2140023 hit a different pathway in the brain called the glutamate system.)

Dopamine probably does play a role in schizophrenia, but other still unexplored factors might be as or more important. The cause of the disease remains unclear. Studies that focus on these neglected unknowns might offer the insights needed to bring about better, faster and more effective drugs, Hyman says.

Another problem that stymies breakthroughs is a heavy reliance on animal models. Scientists often use mice to look for symptoms that can then be applied to human diseases. A mouse that quickly gives up on trying to swim in a tub of water is thought to be despondent. A mouse that doesn't sniff as much as normal around a new mouse is said to be antisocial.

Although these animal behaviors are often the best option for study available, they are a far cry from the human diseases they stand in for, Hyman says. So drugs that can fix these problems in mice don't necessarily translate to people. "Right now, we are in a period of disillusionment with animal models," he says. "People are tired of curing mice."



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YESTERDAY'S DRUGS
A large number of the psychiatric drugs in use today are modifications of compounds developed in the 1950s. Many of these compounds' benefits for treating mental disorders were discovered serendipitously.
Source: S.E. Hyman/Science Translational Medicine 2012

Hyman believes that human stem cell technology might offer a better solution. Ideas — and eventually drugs — might be tested on groups of carefully cultivated human nerve cells in a dish, for instance. Going further, Hyman and others have started talking seriously about small, carefully designed experiments on people (with oversight and consent, of course). In April, a workshop at the Institute of Medicine will explore the idea of testing drugs first in humans.

Brain incognito

Perhaps the largest impediment to the development of new psychiatric drugs is the brain itself. A complex web of interconnected systems constantly altered by the environment, the brain is difficult to study.

Even though it's nestled right in our heads, the brain is hard to reach. A blood pressure cuff can be slapped on for an instant and objective measure of what's happening with the heart. A needle biopsy can physically pull out suspected breast cancer cells for further tests. But when it comes to the brain, there is no easy way to identify and measure the thing that isn't working.

When something goes wrong in the brain, as it does in mental illness, the only outward signs are symptoms. And while these symptoms often signify a particular disease, they are far from perfect indicators. For one thing, a

for these disorders," Insel says. What's needed is a deeper understanding of the brain — the genes, the molecules, the circuits that go awry in some diseases, he writes October 10 in *Science Translational Medicine*. It's much harder to fix something if you don't know what's going wrong.

A reset

The situation is grim, but not hopeless, says Insel. At a time when major pharmaceutical companies are abandoning psychiatric drug development, Insel says he is doubling down, investing federal grant money in places where investors fear to tread. "There are a whole series of pretty amazing developments that I think are worth investing in," he says.

One such project is a newly created funding opportunity for scientists called the Research Domain Criteria, or RDoC. This project has the audacious goal of mapping particular symptoms or behavioral abnormalities to specific causes in the brain. RDoC will bypass the current onerous and problematic disease labels and instead directly investigate what's going on in the brain. Rather than attempting to tie the umbrella disease of schizophrenia to a certain kind of neurotransmitter in the brain, under the RDoC plan a specific part of the disease — hearing voices, for example — might be linked to that neurotransmitter.

Doing small, quick, early-stage trials of prospective compounds in people is another way to move more drugs through the pipeline. In many cases now, a failure in a clinical trial is completely uninformative, Insel says, since it's unclear why a compound failed. By carefully designing studies to test whether a drug hits its target and eases some measurable outcome, these "fast-fail" trials could rapidly identify both promising drugs and ones that don't work. NIMH has requested grant proposals for fast-fail trials aimed at schizophrenia, autism and mood and anxiety disorders.

Some researchers say that the time has come to get back to the roots of psychiatric drug discovery, in which people were given drugs and observant clinicians paid careful attention to the drugs' effects. This is the principle behind the upcoming first-in-humans workshop. And it is the kind of careful observation that can liberate a drug, freeing it to treat problems that it wasn't initially designed to fix. This is how a TB drug and an anesthetic ended up as mood treatments.

Even with many firms pulling back, some pharmaceutical companies are teaming up to work on these tough psychiatric disorders, Kaitin says. Merck and other companies are starting to enter into collaborative agreements with each other and academic centers, spreading the risk but potentially sharing the profits. "I paint a pretty dismal picture when I go out and talk about this, but I think the future is going to be in partnerships and collaborations," Kaitin says.

And of course, more basic experiments on how the brain works will prove instrumental to designing better drugs. If support for that sort of undirected experimentation dries up, so will drug companies' efforts to turn those discoveries into medicine. "At some point, you're going to exhaust the supply," Kaitin says.

Despite the challenges, people are starting to talk seriously about ways to change how psychiatric drugs get discovered, Insel says. "I'm really optimistic," he says. "I think there are great opportunities here."

COMMENTS (3)

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I'm a retired psychiatrist who has utilized most of the currently available medications during my years of practice. The comments about problematic side-effects and incomplete benefit certainly ring a bell with me. The new ideas described in this article sound very hopeful. Thanks for this example of creative thinking and optimism. Grant Syphers, MD

Grant Syphers — Feb. 11, 2013 at 9:39am

Maybe it's too soon but what we may need is another Decade Of The Brain, as we had in the 1990's

MyOtherHead — Feb. 11, 2013 at 9:39am

Given the difference between human brains and mouse/rat brains, it makes sense to test primates, especially humans, rather than mice or rats. I don't see cultivated cells as providing too many better clues simply because those cells won't exist in the body and won't interact with the environment the way that people do. For one thing, those cultivated cells will exist in a 2D environment, whereas the brain is a 3D environment. For another thing, the brain constantly receives inputs from other parts of the body and sends responses to various parts of the body. I suggest that if those inputs and responses are lacking, the brain won't have the same behavior as a brain in a body.

I am glad to see that the testing regimen is being re-evaluated. Pharmaceutical testing in America is one thing that makes our drugs so expensive. The entire process needs to be reconsidered and restructured, not just for psychiatric drugs but for all drugs. Before testing gets too far along, we need to know if the drug is worth a complete, rigorous evaluation. "Fast fail" methodology may be the way to go.

Ultimately, I think we have to come up with a way to carry out human experimentation. Moreover, I suggest that we need serious investment in brain research, and that research needs to be focused on two major areas: (1) understanding how a "normal" brain works and (2) understanding how the brain falls into disease state with an eye towards finding specific, reliable markers of disease.

Robert Woodman — Feb. 11, 2013 at 9:41am

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