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A Dry Pipeline for Psychiatric Drugs

By RICHARD A. FRIEDMAN, M.D.AUG. 19, 2013

Fully 1 in 5 Americans [take at least one psychiatric medication](#). Yet when it comes to [mental health](#), we are facing a crisis in drug innovation.

Sure, we have many [antidepressants](#), antipsychotics, hypnotic medications and the like. But their popularity masks two serious problems.

First, each of these drug classes is filled with “me too” drugs, which are essentially just copies of one another; we have six S.S.R.I. antidepressants that essentially do the same thing, and likewise for the 10 new atypical antipsychotic drugs.

Second, the available drugs leave a lot to be desired: patients with illnesses like [schizophrenia](#), [major depression](#) and [bipolar disorder](#) often fail to respond adequately to these medications or cannot tolerate their side effects.

Yet even though [25 percent of Americans](#) suffer from a diagnosable mental illness in any year, there are few signs of innovation from the major drug makers.

After a series of failed clinical trials in which novel antidepressants and antipsychotics did little or no better than placebos, the companies seem to have concluded that developing new psychiatric drugs is too risky and too expensive. This trend was obvious at the 2011 meeting of the American Society for Clinical Pharmacology and Therapeutics, where only 13 of 300 abstracts related to psychopharmacology and none related to novel drugs. Instead, they are spending most of their research dollars on illnesses like [cancer](#), heart disease and [diabetes](#), which have well-defined biological markers and are easier to study than mental disorders.

To understand this predicament, it helps to know how we got here.

All of our current antidepressants, antipsychotics and anti-anxiety drugs share the same molecular targets in the brain as their prototypes from the 1950s. For example, the new antipsychotic drugs block [dopamine](#) receptors in critical brain regions, just like the first antipsychotic, Thorazine, synthesized in 1950. And all of our current antidepressants increase the levels of one or more of the neurotransmitters serotonin, dopamine or norepinephrine, just like the early tricyclic antidepressants.

With rare exceptions, it is hard to think of a single truly novel psychotropic drug that has emerged in the last 30 years. True, the new psychotropic drugs are generally safer and more tolerable than older prototypes, but they are no more effective. So why has the pharmaceutical industry churned out so many copycat drugs?

The simple answer is that we don't yet understand the fundamental cause of most psychiatric disorders, in part because the brain is uniquely difficult to study; you can't just [biopsy](#) the brain and analyze it. That is why scientists have had great trouble identifying new targets for psychiatric drugs.

Also, knowing how a drug works in the brain doesn't necessarily reveal the cause of the illness. For example, just because an S.S.R.I. antidepressant increases serotonin in the brain and improves mood, that does not mean that serotonin deficiency is the cause of the disease; many depressed patients get better with medications that have no effect on serotonin.

Until very recently, scientists have relied on the same animal models to screen for potential psychotropic drugs that had been used for decades, which predictably yielded a raft of "me too" medications that shared the same mode of action as the old drugs.

Sure, this old method of drug development has produced commercially successful blockbuster drugs, like the antipsychotics Seroquel and Abilify. But soon the patents on these medicines will expire, and there is little new in the pipeline.

Perhaps, though, the pharmaceutical industry is making a mistake, running away from the brain just when things are getting interesting. Consider ketamine (known on the street as Special K), an anesthetic agent that has recently shown unusually powerful antidepressant effects.

Ketamine acts on a target in the brain where no other drug in psychiatry currently does: the NMDA receptor, which it blocks. The receptor is the site of action of glutamate, a neurotransmitter critically important in learning and memory — and, it turns out, in [depression](#).

Several promising early studies found that depressed patients who had failed to respond to multiple antidepressants [experienced rapid resolution of their symptoms](#) within a few hours of ketamine infusion.

Unlike standard antidepressants, which typically take weeks to work, ketamine's effect is rapid because its target, the NMDA receptor, is fast-acting. But this is a tricky biological system to modulate: too little glutamate function at this receptor can produce [psychosis](#), and too much can kill neurons.

Whether ketamine, or a similar compound, will ultimately prove safe and effective as an antidepressant is unclear. Presently, though, the pharmaceutical industry has little taste for the long-term financial risk of discovering new psychotropic drugs.

In contrast, academic researchers, who are not beholden to shareholders, are much freer to do high-risk, high-gain experiments that can fail. Large multisite research programs like the [Brain Activity Map](#), along with the latest gene-sequencing technology, can help identify the circuits and genes that are linked to various psychiatric disorders and find promising new targets for drugs. These discoveries, in turn, may entice the drug makers to reinvest in psychiatric drug development.

As consumers desire new treatments, they have to recognize that innovation carries risks. Drugs are approved by the Food and Drug Administration on the basis of short-term studies, so there is always limited knowledge about the long-term safety of new medications. This is particularly true for drugs that act on new targets in the brain about which relatively less is known.

But if we are to find better medical solutions for the mental illnesses that disrupt and destroy so many lives, we need to acknowledge a simple truth: there can be no innovation without financial — and medical — risk.

Dr. Richard A. Friedman is a professor of clinical psychiatry at Weill Cornell Medical College.