

IN SESSION with Stephen M. Stahl, MD, PhD

The Future of Novel Drug Discovery in CNS



Dr. Stahl is adjunct professor of psychiatry at the University of California San Diego and chairman of the Neuroscience Education Institute. He was recently elected as an Honorary Visiting Fellow in the department of psychiatry at Cambridge University (UK). Of his many affiliations and accomplishments, Dr. Stahl serves as a fellow of the American College of Neuropsychopharmacology as well as the International College of Neuropsychopharmacology, where he was formerly vice president. Dr. Stahl's major interests are dedicated to producing and disseminating educational information about diseases and their treatments in psychiatry and neurology, with a special emphasis on multimedia, the internet, and teaching how to teach.

Is there a need for more effective and better-tolerated psychiatric medications?

Absolutely. There are signals of efficacy in medications that are approved, of course, but it always comes at a cost. We need to improve both the efficacy signal and reduce the cost in terms of side effect burden.

Are there any promising investigational agents already approved for nonpsychiatric indications that might eventually be shown to have real therapeutic value? What do we know about their presumed mechanisms?

There are not very many. I think the problem is that the pace of innovation has slowed throughout the industry, so the non-psychiatric medications are just as much in kind of a drought as are the psychiatric medications. Some anticonvulsants are either approved or just about to be approved. Although they have not all been studied for bipolar claims, this is generally where psychiatrists have mined the fields for new bipolar medications. We do not really know how drugs stabilize mood, except we know that some, but not all, anticonvulsants do.

One anticonvulsant that is being tested is ganaxolone, a neurosteroid. It is only in trials at this point, and does seem to have a signal

for epilepsy, but it also has some theoretical value, potentially, for post-traumatic stress disorder. We really need an effective medication for that condition. It works on γ -aminobutyric acid (GABA) receptors—but the so-called extra-synaptic nonbenzodiazepine-sensitive ones that are maybe setting the tone of the GABA neurotransmission.

Tetrabenazine, for Huntington's Chorea, could possibly be used for treatment-resistant psychosis, though it is quite expensive because it is an orphan drug. Vinyl GABA is an approved anticonvulsant, but because it is potentially toxic, one needs to study it carefully.

Two serotonin (5-HT)_{2A} antagonists, may be approved for sleep. Eplivanserin will be called Cilytri if it gets approved. The other, pimavanserin, has actually been studied for an add-on to antipsychotics for schizophrenia. Both of those agents have been studied in Parkinson's disease psychosis. Perhaps they may find a role in anxiety disorders, sleep disorders, mood conditions, and so forth.

Do topiramate or levetiracetam have any psychotropic effects?

There were two double-blind trials of topiramate that failed. This occurred around the same time topiramate went generic, so researchers never went after it further and, with the somewhat underwhelming results, dropped it.

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Levetiracetam has never really had large trials. There have been some indications in small groups of patients, but no compelling evidence in bipolar disorder. It is very interesting that these two drugs do not work the same as lamotrigine or carbamazepine. Certainly, in a general sense, they work on ion channels, but topiramate is a pretty good migraine drug and it is an anti-epileptic. Levetiracetam works on synaptic vesicle protein, very unique to any other mechanism. Although it, too, is an anticonvulsant, the question is whether these mechanisms work in bipolar disorder. Being an anticonvulsant does not ensure that a drug will be a mood stabilizer. Topiramate and levetiracetam are indications of the fact that not all anticonvulsants are mood stabilizers.

Even drugs like pregabalin and gabapentin, which work very well for seizures, pain, and even anxiety, are not robust mood stabilizers. They work on $\alpha 2\delta$ protein of a calcium channel. Some of these other mood stabilizers may work more powerfully on certain types of sodium channels, but there must be at least nine types of sodium channels. Researchers must then find out which of these sodium channels mediate the therapeutic actions, and which might actually mediate the side effects like sedation. We need agents that at least retain the efficacy, if not reduce side effects. This has been a pattern of much innovation in the field of psychiatry.

Based on what we know, are pharmacologic investigators adopting more rational approaches to drug discovery? Are they now using any information about genes and proteins that are involved in the disorders themselves?

I wish I could say robustly yes, but I fear the answer is still some serendipity and, if you will, exploitativeness of further old targets. For example, the Human Genome Project originally promised to find many new targets for drug therapy, with the original thought that there were ~100,000 genes. Not only was this wrong and the number of human genes reduced to 30,000, but of these, there is estimated to be only a few hundred “drugable” targets. In addition, drugs that act at targets other than those for monoamines are often ineffective. Although one would certainly think that the non-monoamine neurotransmitters are important in the brain, it has proven very difficult to get an effective therapeutic agent based on non-monoamine targets such as peptides.

Finally, the gene sequence may not be the issue for therapeutics, but rather the epigenetics. Silencing and activating genes is a theoretical idea, but quite frankly, I am not sure we know which ones to silence or activate.

What has happened is that as we approach the anniversaries of the all these neuropsychopharmacology groups that started 50 years ago, we are in a bit of a drought. We have exploited the monoamines about as much as we can, and it is very difficult to see how a new monoaminergic mechanism would be a breakthrough. The question then is, where else is there

to go? Researchers may empirically target non-monoamine mechanisms, but I am not sure how rational they are as novel therapeutics other than the fact that these non-monoamine mechanisms function in the brain and that if you modify them you might possibly change psychiatric symptoms. That goes without saying. However, to prove that there is a pre-existing abnormality which the drugs are correcting or compensating, still largely does not exist in the field of psychiatry. In other words, we know how the drugs work much better than we know how the diseases work.

Are we going to be looking at the so-called “multi-functional agents” in the near future?

I think we have come full-circle in that we managed to think and fool ourselves initially that many drug mechanisms were dirty and selective mechanisms were great. We actually even convinced ourselves that selective serotonin reuptake inhibitors (SSRIs) were selective. However, not only do most SSRIs have a secondary non-serotonergic property, but the so-called increasing of “serotonin selectively” acts on 14 receptors.

Serotonin has many different actions and is not really all that selective. What is happening now is that norepinephrine is being added in with serotonin to make serotonin-norepinephrine reuptake inhibitors (SNRIs), and then dopamine is added to make triple reuptake inhibitors. Most of the new drugs in development are either SSRIs plus, SNRIs plus, or triples plus. Of the triple reuptake inhibitors, several have tried and failed, but some are going forward.

Two drugs are in late trials as SSRIs plus 5-HT_{1A}: vilazodone and Lu21004. The question is whether they are better than an SSRI alone. There is hope that these drugs will reduce side effects, but with these drugs researchers are not necessarily looking to improve efficacy.

Lu24530, which is not only a triple reuptake inhibitor, but a triple plus, could have more efficacy, at least in theory.

Flibanserin, a 5-HT_{1A} agonist, and 5-HT_{2A} antagonist, is being studied for treatment of the controversial hypoactive sexual desire disorder.

For innovation, chemists put an ordinary mechanism in the drug and add a special mechanism, hoping that the extra mechanism offers either more efficacy or somehow mitigates side effects. That is where I think the field is going. I doubt very seriously whether magic bullet types of drugs will come forward in the central nervous system field.

Is it an unusual case where a single drug fixes a disorder?

Absolutely. This is already done for bipolar disorder, very rapidly. One of the new paradigm shifts I see afoot in the area of major depressive disorder (MDD) is, given the paltry remission rates with first-line treatments, to treat from the very get-go with

two or three drugs. Historically, practitioners have prescribed drugs in sequence, and then finally added one if they failed.

This is taking a chapter out of the book written by cancer chemotherapy or HIV, where unsatisfactory monotherapy results very rapidly got that field to multiple therapies. This is already done for bipolar disorder, very rapidly. Maybe we should begin thinking about it even for MDD—what I call “intramolecular polypharmacy.”

Is there any research that can explain the loss of efficacy of antidepressants in a person over time?

I think the phenomenon may also exist to the extent that antidepressants increase cycling rates. It is a common observation that drugs that work for so-called bipolar types of cases will help mitigate or possibly prevent this loss of efficacy.

I also think this is not a psychological phenomenon but a biological one. The most common explanation would be some sort of desensitization of receptors. The downstream effects of these drugs are chronic, and the brain is always trying to undo a force upon it. This is called homeostasis. If you push on the brain, it pushes back. If it does so successfully, it might actually, if you will, sabotage its own improvement.

I think that administration of two or three drug mechanisms prevents any single one of them from actually desensitizing. This goes right back to the multifunctional drug approach.

Have any drugs really impressed you as being a starting point for the development of new categories of medications?

There is something in the glutamate pharmacology that gives it the potential to be a breakthrough in the area of mood disorders. Having said that, it has always surprised me why ketamine, which can cause a schizophrenia-like syndrome, can help treatment-resistant depression. Investigators explain that ketamine may work by nonspecifically “rebooting” the brain mood system, sort of like rebooting a crashed computer. More specifically, the anesthetic ketamine blocks a certain type of glutamate-receptor, *N*-methyl-D-aspartate (NMDA). Despite blocking NMDA receptors, ketamine paradoxically increases glutamate release downstream. It does this by blocking NMDA receptors on inhibitory GABA interneurons, leading to disin-

hibition (ie, increasing) glutamate release. It is interesting that more and more of these ketamine infusion studies are coming out in the treatment of depression and suicidal symptoms. Some studies are even beginning to correlate improvement in depressive and suicidal symptoms with changes in neuronal activity in the anterior cingulate cortex.

In addition, lamotrigine may have something to do with riluzole, and both may decrease glutamate release. One way to block glutamate by blocking its NMDA receptor, like ketamine does. Another way to do it, like lamotrigine and even riluzole do, is to prevent the glutamate from even getting out so it does not work on any receptors.

There are 14 serotonin receptors, and who knows how many subtypes of glutathione receptors; of the latter, one that seems to be a target is NR2B. The drug traxoprodial, also known as CP-101606, and others, seem to work at the NR2B receptor as an antagonist, much more selectable than ketamine. This suggests that veering away from the monoamine systems to the glutamate system may uncover something unexpected and robust.

Back to my original point, the question is, why you would not want an SNRI in that same molecule. Because again, I am sure that these NR2B antagonists or ketamine-like drugs will not be perfect, and they are likely to be added on anyway. Thus, one of the ways to actually get a really amazing drug would be if the chemist provides NR2B antagonism with serotonin and norepinephrine reuptake blockade. This is the direction in which the field may be going.

Do you anticipate any current therapies crossing over and getting Food and Drug Administration approval for psychiatric use? Is there a timeline when we will get a completely new kind of drug out?

I do not see a whole lot of crossovers from other therapeutic areas in the near future, unless we can find drugs in one therapeutic area or another with a peptide mechanism of action. So far, peptide active corticotropin releasing factor 1 antagonists have failed in depression and anxiety, as have other peptide targets including substance P and other neurokinin antagonists, cholecystokinin antagonists, and neurotensin antagonists.

Glutamate is probably the most promising, if one could add that to monoaminergic mechanisms. I think that could even happen in the next 5–10 years. *PP*