What are the most pressing challenges--and exciting developments--in psychopharmacology? In psychiatry clinical trials?

In conversation with... Andrew J. Cutler, MD

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Dr. Opler: Dr. Cutler, could you tell us a bit about how you got into our field, what your research focus is, and why it matters? What is it about our work that inspires you?

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Dr. Cutler: I always wanted to be a doctor. My father was a physician, and I grew up loving biology and science. I also loved detective stories like Sherlock Holmes and even Encyclopedia Brown when I was young. So when I went to medical school, I imagined myself going into internal medicine, which I saw as detective work. You get the data and you make the diagnosis, which is like solving a mystery. Then I took neuroscience and neuro-anatomy, and I realized that the brain is the most interesting organ in the body. When I did my psychiatry rotation, I really fell in love with psychiatry, especially brain chemistry. This was at the dawn of the modern psychopharmacology era. So I was really excited about these new developments and new medicines that were coming out that seemed to promise even better efficacy and safety.

I was at the University of Virginia at the time, and I decided to do a combined internal medicine and psychiatry residency. I ended up getting board certified in both. Along the way I also did research training on dopamine receptor pharmacology. I wanted to do research and be a professor. That's where I saw my career going.

I started out my academic career at the University of Chicago doing psychopharmacology research. I discovered it was difficult being junior faculty. My research kept getting put on the back burner. Then I was recruited to a hospital in Orlando, Florida, that had a psychiatry division and wanted to do clinical trials. So I went there and started doing clinical trials privately. My goal was to do academic quality research in a private setting with best business practices--and less bureaucracy.

I really caught a wave because that was a time when a lot of pharmaceutical companies were looking at doing research in private

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***Dr. Cutler**, a member of WCG's Scientific Leadership Team, shared his insights during a recent conversation with Mark Opler, MD, PhD, chief research officer at WCG-MedAvante-ProPhase. Dr. Cutler is chief medical officer for Meridien Research and a courtesy assistant professor of psychiatry at the University of Florida.*

The interview has been edited for clarity and length.

settings. It was one of those lucky "right place at the right time" kind of things.

I'd say my primary research focus has been an outgrowth of my dopamine receptor research. The four areas clinically that involve dopamine dysregulation that I've done work, and published, in are schizophrenia, bipolar disorder, depression, and ADHD.

This matters personally to me: Not only because of the patients I have met along the way, but I also have a lot of family members with mental illnesses including bipolar disorder and ADHD. Some small part of me hopes to find great treatments to help them and others.

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Dr. Opler: Specifically, what do you see as the top three challenges in our current trial methodologies and the execution of studies?

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Dr. Cutler: This is my 26th year of doing clinical trials; over that time, they have become a lot more complicated. Of course, the problem we have, especially in CNS drug development, is separating drug from placebo. We're trying to detect a signal and minimize noise. Over the years, what has happened, not only in the U.S. but across the world, is we're seeing placebo response rising. The problem in the U.S. is we're not only seeing placebo response rise, we're actually seeing drug response drop.

There are many reasons for this.

One of the problems is identifying the appropriate patient and, even more than that, the appropriate biological target, for your potential intervention. The problem in psychiatry is the brain is so darn complicated. We're forced to use diagnoses that are clinical diagnoses, and not necessarily biologic targets. So over time, I have seen many interesting and unique drugs fail--although they probably work well for a subset of people with a particular clinical condition--for instance, schizophrenia. I like to say, it's not schizophrenia but schizophrenias. There are many different pathologies here. It's not only a failure of the drug, it's a failure of our ability to select the right patients that have the target we're aiming for.

Another challenge we face is minimizing noise. The problem is, of course, is people have been chasing this smaller signal. So they've done things like ramp up the number of patients and the number of sites in a study. Paradoxically, this introduces more noise, making it even harder to detect a signal.

Along those lines, we had a lot of issues with payers for new treatments. Early on, companies are asking, "How do we start generating data that's going to help us get this medication paid for in the marketplace." That's a very reasonable thing. Meanwhile, they're also focused on marketing considerations that end up adding measures such as quality of life and healthcare economics and things like that. But again, what we're trying to do is detect a signal. The more of these kinds of outcomes and variables that get put in, the more potential noise gets put into the system. That's something I think about and worry about as well.

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Then there is integrating technology. We all know technology is going to change what we do in clinical trials. We just don't know how yet. There is a variety of these emerging technologies I think people are trying to figure out.

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Dr. Opler: To shift gears a little bit--it's been a remarkable past 12 months. What are the developments you think are most exciting, and how do you think it will have an impact on the lives of our patients?

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Dr. Cutler: I have to agree. I'd like to say that the past year or two has made me the most excited I have been about clinical trials in CNS and psychiatry since I got started all those years ago.

I've been thinking about the development of technology such as wearables, which allow you to collect so much more data in a less intrusive way. Not just activity level and sleep, but even monitoring cell phone usage and social media activity. How many phone calls are you making? Are you getting more active? Wearables are going to revolutionize not only research, but people's lives.

I am excited about two areas in the field of depression. For a long time, we focused on medications that are basically ways to manipulate the three classic monoamines: serotonin, epinephrine and dopamine. We've gone at it in different ways, but the treatments have not worked well for a lot of patients. Finally, in the past year or two, we have had some very positive data come out on a couple of very different mechanisms.

One of them is esketamine, which is inhaled nasally. This works through the glutamate system, a totally different chemical. Janssen has that, but other companies have other kinds of glutamate-type, ketamine-like drugs.

Sage has a drug that is working on Gaba A receptors. Glutamate and Gaba are the two predominate chemicals in our brain. Glutamate is the major excitatory nerve transmitter. Gaba is the major inhibitory nerve transmitter. Both have been shown to have rapid effects--I'm talking hours--a day or two at the most. Traditionally, with the monoamine medications, you have to wait several weeks to see anything. So I'm really excited about this possibility of helping a lot more patients get better faster.

The other therapeutic area that's really exciting to me right now is schizophrenia. Very positive results on a study with a very different mechanism of action were recently announced: a drug that works through receptors called TAR 1 receptors--trace amino receptors. This is a chemical system in the brain that has recently been discovered.

There's one other thing I should mention: In 2017, we had two new drugs approved to treat tardive dyskinesia, which is a consequence of our antipsychotics. These work through a very interesting mechanism called VMAT2 inhibition. Most of our medicines work on the outsides of cells; this one works inside. That opens the door to possibilities.

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Dr. Opler: What's coming next? What do you see as the top three opportunities in clinical development in neuroscience?

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Dr. Cutler: In addition to further developing this idea of rapid onset, or rapidly acting anti-depressants, I think we have to refine that quite a bit. We need ones that are, ideally, taken orally and have less risk and toxicity. Some of these rapid treatments now are intravenous.

We have a huge need for the treatment of schizophrenia in general and especially those symptoms that are most impairing-- negative symptoms and cognitive impairment. These are the symptoms that keep someone from meaningfully engaging socially or occupationally. Schizophrenia is an especially pernicious illness because it hits people in their late teens, early twenties right when they're getting ready to launch into their life.

As science evolves, I think we might be making progress. I was recently on an advisory board with a company that has developed a new medicine that is in front of the FDA right now. It has some very interesting intercellular mechanisms and may indirectly be affecting the glutamate system. That may help some people with schizophrenia who haven't previously been helped.

The other one is in the ADHD field, which is another interest of mine. What the world needs, I like to say, is a non-stimulant that actually works reliably because we do have stimulants that are very effective, but they come with significant baggage--things like abuse and diversion as well as significant cardiovascular risk. There are a couple of non-stimulants that I'm excited about.

Another big need is bipolar depression. We have many approved to treat mania, but not for depression. And bipolar disorder is an illness predominately of depression. More depression, more recurrent depression and that's what holds people back. We really need more effective treatments and more options for the depressive phase in particular.

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Dr. Opler: To finish up, let me ask you about your predictions. Are there particular programs that you are excited to see read out one way or another in the next 12 months?

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Dr. Cutler: One area I haven't talked about yet is digital therapeutics. What that means is actual digital treatments, digital interventions. One that we're working on for ADHD is a video game that is developed based on the principles of neuroscience that adapts as the child -- or even adult --plays it. This video game has been used for ADHD, but it is starting to be looked at for autism and for adults with Alzheimer's-related dementia. So as a person interacts with the game and plays the game, the game adapts and gets a little harder and more

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challenging. Theoretically, what you're doing is training the brain and developing and strengthening circuits of attention and potentially inhibiting unwanted impulses. It's almost like you're working out your muscle. You lift weights, you work out your muscle. You can gradually lift more and more. So I'm very excited about that kind of possibility. For so long we thought of treatments and medications as pills. But obviously, we can administer medications intravenously, intranasally, as patches and various other ways. But potentially, we can have interventions and treatments that are digital and not a medication. These are things that are coming right now.

And as I mentioned, wearables also fascinate me. There is a wealth of data and information there that we can use that may lead to further treatments, further ways of monitoring the treatments, that maybe unlock some more of the clues and mysteries of how the brain works.

One other quick thing about technology: There is a technology that is not brand new, but it is being used increasingly. It assists in measuring improvement in patients on medications. It may detect changes even before the patient notices anything. One of those is a facial-recognition software. Patients who are depressed have something called negative cognitive bias, so everything seems more negative. If they look at a picture of a face that's neutral, they will often misinterpret it as sad or anxious. Now if someone is given effective medication, they can more accurately identify the emotion of the face within a day or two, well before they notice feeling better. So I think about the potential of this to identify someone who is responding or potentially going to respond well to a treatment early on, then you can stay on the right track. Then if they're not responding, rather than having to wait and potentially have the illness progress, maybe we can switch treatments and do something else.

Another way of applying this is something I heard about a couple of years ago. Computers can analyze people's voices and accurately predict if someone is going into a depressive episode or becoming psychotic. So potentially we can catch people before they slip into a serious mental state that makes it harder to treat. Maybe we can do things prophylactically or very early on to prevent negative consequences. That's very exciting.

Interviewee

Dr. Cutler is a member of WCG's Scientific Leadership Team, and a recognized expert in CNS therapies and clinical trials. Dr. Cutler is a sought-after speaker about the evaluation and treatment of mental illnesses such as ADHD, Bipolar Disorder (Manic-Depression), Major Depression, Anxiety Disorders and Schizophrenia. He conducts clinical trials for Phase I-IV studies. Indications include ADHD in children, adolescents and adults, depression, anxiety, bipolar disorder, schizophrenia and other neuropsychiatric and medical conditions. In addition to being the Chief Medical Officer for Meridien Research, Dr. Cutler is a Courtesy Assistant Professor of Psychiatry at the University of Florida.

Interviewer

Mark Opler, PhD, MPH, serves as Chief Research Officer, directing scientific research and development at WCG's MedAvante-ProPhase. Dr. Opler was the founder of ProPhase and served as its CEO and Chief Scientific Officer among other positions. He holds the titles of Adjunct Assistant Professor of Psychiatry at New York University and Assistant Professor of Clinical Neuroscience at Columbia University's College of Physicians and Surgeons.