What are the most important trends in CNS clinical trials? What lies ahead in 2019 and beyond?

In conversation with... Christoph U. Correll, MD

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Dr. Opler : Tell us a little about how you got into this field and what your research focus is.

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Dr. Correll : I'm a clinical psychiatrist and clinical scientist. I actually entered psychiatry for two reasons. First, because there are four psychoanalysts in my family. I thought it must be important to try to dissect the brain in a certain way, but I soon realized that just talking doesn't really do the trick. So I focused more on biological psychiatry and psychopharmacology. The other reason is that, during my medical school years, I worked on a locked unit, one-on-one with patients. I found psychosis fascinating: I got into the field wanting to try to solve the riddle of schizophrenia, to understand it and potentially cure it. I've obviously become wiser; now it's about just pieces of it–maybe helping patients live with it better and developing therapeutics that can ease some of the suffering and improve some functionality. My research is focused on early recognition and prevention of psychosis, as well as psychopharmacology, and the comparative effectiveness of treatments.

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Dr. Opler : Could you tell us what you see as the top three challenges in our current clinical trials environment?

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Dr. Correll : Unfortunately, we've seen many programs look promising but ultimately fail. The transition from Phase II to Phase III has been particularly difficult, and we need to understand that better. We get signals in smaller trials that are suggestive, but once they go into large explanatory Phase III trials, the results are disappointing.

One of the related big problems is the rising and enormous placebo effect that has really invaded and undermined the signal-to-noise detection. We've seen recently meta-analyzed that: In schizophrenia, over the 45 years, the placebo effect has increased by 12.2 points and the drug effect by 1.2 points. When you have more and more sites and

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Christoph U. Correll, MD, *a member of WCG's Scientific Leadership Team, shared his thoughts in a recent conversation with Mark Opler, MD, PhD, chief research officer at WCG-MedAvante-ProPhase. Dr. Correll is both a clinical psychiatrist (for both adults and children) and a clinical scientist. His work focuses on the identification, characterization and treatment of adults and youths with severe psychiatric disorders. His particular area of expertise is psychopharmacology.*

The interview has been edited for clarity and length.

more study arms, the placebo response increases; we really need to get that under control. Perhaps there is more expectation bias–and maybe some baseline inflation. We need to have methodology that can deal with that. I think that's a major challenge.

Another challenge is that we see patients intermittently and, based on their recall, we make judgments on how they actually behaved, what they felt and what they thought over a week or even longer. It's still very subjective. We need a methodology that can get a much finer-grained assessment and also more objective data, on behavior and the performance of patients.

A related one is cross-cultural psychiatry. We're now getting approvals in many cultures, and psychiatry might be more culturally bound than we think. In some cultures, the placebo effect is even larger; especially when you only have a couple of patients per site. How do we deal with that? Researchers haven't really tapped into that.

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Dr. Opler : Thank you. Could you share with us a couple of examples of developments in clinical research from the past year that you are particularly excited about?

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Dr. Correll : I think the most exciting area at the moment–because approval appears to be right around the corner–is harnessing a glutamate system for depression. We're seeing rapid-acting antidepressants. Esketamine is on the forefront, including as an IV and now as an intranasal treatment. We've learned that our hypothesis--that it takes several weeks until depression improves–is not necessarily right. If you have another receptor system and another approach, people feel better 40 minutes after a single IV dose–and achieve the maximum affect after a day or two. That's really exciting. Also, it is anti-suicidal; that opens different treatment paradigms. People who are currently helped in emergency rooms and are sent for admission could maybe be spared the admission. We actually get "speed jumps" into improvement and faster recovery.

Related to that is, we have basically now, for the first time in 40 or 50 years, an opening into different receptor systems. In psychiatry, it's always been around serotonin or adrenalin or dopamine. Now, we can harness receptors related to abuse with ketamine or cannabinoids seeing–and benefit the patient. That's what I'm excited about.

Another important development–one that's underappreciated–is that we can we use more technology to both assess and treat patients. Patients–and people in general–use technology all day, for many, many hours. Getting information for clinical trials from either the e-mental health tools that can be used as medical devices or maybe devices that measure and improve adherence. This is something I'm most excited that this could yield additional benefits for patients.

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Dr. Opler : What do you see as the top three opportunities in clinical development for psychiatry? Where can we make a dent?

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Dr. Correll : I just mentioned the use of technology. Wearables provide the opportunity to gather more objective data–and to perform interactive assessments and momentary assessments. This will help us determine whether patients actually hear voices all of the time vs. only saying it when we have them at baseline. During screening, this could actually refine the patient population we want to enroll, based on frequency and severity of certain symptoms. I think that's exciting.

Another challenge is this: The field must move away from these broad-stroke diagnostic approaches for molecules. We must re-stratify medicine and stratify clinical trials. When a medication has a target engagement, let's say an alpha-7 agonist in the nicotinic system, you want to see whether you can actually measure that system and only enroll patients who have the deficit.

For people who use an anti-inflammatory drug just measure people with inflammation and enroll those patients. But what the companies are still doing is, they have a hypothesis, they take all patients and then run their biomarker afterwards–when it's totally underpowered-- to see if it could have yielded a result. I think that's something where we really need to get into subgroups of patients. We might also need to reanalyze some data to see who are the super-responders; we can learn from even failed trials by identifying the potential subgroups.

These are two areas where progress can be made quickly. Other than that, obviously, I would say we need mobile mechanisms. We need also treatments for dimensions that are not captured in the current treatment algorithm, such as negative and cognitive symptoms for people with schizophrenia, treatments for the elderly who are agitated and aggressive, and treatments that have lower risks for increased mortality. These are lower-hanging fruit than, for example, understanding and treating dementia.

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Dr. Opler : As we wrap up, could you share with us some of your predictions for what we can expect for 2019. What do you think some of the surprises are going to be in the coming year?

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Dr. Correll : I don't think there will be a big paradigm shift or huge surprises. One year is just too short a time–otherwise we would have seen bigger movements or rumblings already. But there's a steady flow of programs, some of them that will read out. For example, more data on esketamine will also be most likely presented to the FDA; we'll see whether there will be approval for it and for which indications. There will also be the read outs on Lumateperone for different indications than schizophrenia--for example, bipolar depression or one of the studies

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of its use in the elderly. Most likely Lumateperone–which provides selective and simultaneous modulation of serotonin, dopamine and glutamate–will get FDA approval in 2019; it will be one of the safest anti-psychotics.

It will be interesting how the MIN-101 study will fare; that might take much longer than 2019.

What about the story of 5-HT(2A) inverse agonism–that will be interesting. We may get some readouts on the pimavanserin augmentation study in schizophrenia for negative symptoms and also for treatment of depression. (Pimavanserin, a selective serotonin 5-HT[2A] receptor inverse agonist, targets 5-HT[2A] receptors while avoiding activity at dopamine and other receptors commonly targeted by antipsychotics.)

There will be a readout on the antipsychotic ALKS3831. It should provide insight into whether adding samidorphan to olanzapine will reduce weight dramatically–and whether it is just the weight reduction or if there are also cardio-metabolic effects that are relevant for patients.

It's good stuff, because–except for advancements the VMAT-2 inhibitors for treatment of tardive dyskinesia–we haven't seen many approvals of novel mechanism agents in CNS. Seeing some studies and programs that work out is reinvigorating the field. That's important, because many pharmaceutical companies have moved away from studying the brain; it's good to see that there's room for further development.

Interviewee

Christoph U. Correll, MD. is a Professor of Psychiatry at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and Medical Director of the Recognition and Prevention (RAP) Program at the Zucker Hillside Hospital in New York. Dr. Correll's research and clinical work focus on the identification, characterization and treatment of adults and youths with severe psychiatric disorders.

Interviewer

Mark Opler, MD, PhD, serves as Chief Research Officer, directing scientific research and development at 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.