What are the most pressing challenges in psychiatry clinical trials? How are scientists addressing them?

In conversation with... Dr. Michael Liebowitz

wcg™

Q

Dr. Opler: Dr. Liebowitz, thank you so much for joining us here today. I'd like to begin by asking you to give us a brief personal introduction. Tell us a little bit about yourself, how you got into this field, and why it matters; why it's important to you.

A

Dr. Liebowitz: Well, as you know, I've been in the field for a long time. I worked at Columbia in the New York State Psychiatric Institute in the late 1970s. I was a resident in psychiatry–the psychoanalytic model was really dominant during that time. I worked on a long-term inpatient unit where we had a lot of young people who tried to go off to college but became very anxious and panicky; they dropped out of college and came home. They would be hospitalized at the unit for up to two years; their condition would be treated as a failure of separation and individuation with long-term psychoanalytic psychotherapy.

It was a very warm, humane setting, but I didn't see a lot of progress. I had a medical background–I'd been interning in internal medicine, and I brought a bit of that perspective to psychiatry.

And then I went to a conference on borderline disorders out in Topeka, Kansas; it featured several prominent psychoanalytic speakers. One psychopharmacologist, Dr. Donald Klein, spoke about treating panic disorder with something called Imipramine–at that point, a new antidepressant–and treating certain kinds of depression with MAO-inhibitors. I found that very interesting.

I went back to Columbia and I started trying to use the Imipramine with some of the patients on the long-term inpatient unit, and they got better and left the hospital in a matter of weeks and months rather than struggling for years. I said, "Wow. I've got to go work with this guy." But the next year the mountain came to Muhammad because Dr. Klein came to Columbia in my PGY-4 as the director of research. And when I finished my residency, I had the opportunity to work with him along with Fred Quitkin, Pat McGrath and John Stewart. We then started what was probably the first clinic in the country to specialize in anxiety disorders.

Continued >

Dr. Michael Liebowitz, *a member of WCG's Scientific Leadership Team, shared his insights during a recent conversation with Mark Opler, PhD, MPH, chief research officer at WCG's MedAvante-ProPhase. Dr. Liebowitz, a pioneer in social anxiety disorders, is a Columbia University psychiatrist and founder of the Anxiety Disorders Clinic, the first of its kind, at the New York State Psychiatric Institute. He also developed the Liebowitz Social Anxiety Scale (LSAS).*

The interview has been edited for clarity and length.

We continued Dr. Klein's work in panic, but I became more involved in the area of social anxiety. That's a long story, but essentially, we took something that was thought to be just performance anxiety and found out that it was much more pervasive and chronic and disabling, extending to all kinds of interpersonal interactions. And that led to the grouping of social anxiety disorder to the generalized form in DSM-3R and DSM-4. It also led to a lot of work with trial design, ranging scales, and psychopharmacological treatments. Then we collaborated with behavioral therapists–which really hadn't been done before–in joint studies and competitive studies. That opened up a whole new area in the field.

So, that's my background during the 1980s and 1990s. It was an immensely productive and rewarding time.

Q

Dr. Opler: Listening to your descriptions of some of these paradigm shifts in psychopharmacology and psychiatry, it leads me to think a little bit about the paradigm shifts happening right now in our field. With that in mind, what thoughts do you have about the challenges that we're facing today?

A

Dr. Liebowitz: One of the things that was enormously productive for us at Columbia was open clinical trials, where we had the ability to test an initial hypothesis. For example, when fluoxetine came on the market the initial dosage of Prozac was 20 mg for depression and we wanted to see if it'd work as an antianxiety drug as well. We gave the patients all Prozac 20 mg and a few of them dropped out of the trial within a few days because their anxiety got worse not better. What we found was that the dose was too high. We started opening these capsules and dissolving them in water and giving people 2.5 mg and 5 mg; the drug worked very well. You have to escalate it slowly.

Then that led to some controlled trials with 10 mg Prozac and liquid Prozac which has been very useful for countless numbers of anxiety patients. Similarly, when you conduct a small open trial, you can refine your target population, you refine the use of the drug, and you get a feeling of what the side effects are, how fast you can escalate it, what a good dosage is, or what's too high a dose. That's harder to do these days.

So, one of the real challenges is poor trial design These big phase 2 trials–they're controlled trials which are supposedly are more rigorous and confirmative. But you don't learn how to use a drug in a double-blind trial. You don't know what you're giving, and you can't escalate up and down. So, that's a huge issue right there. And then there's the fact that current studies aren't, for the most part, informed by what's worked well in the past.

Another issue is competitive enrollments. I think it causes us to be fast and sloppy; we're always worried if we don't put patients in quickly somebody else is going to do it first. You know, you should set up a site, contract what you think is reasonable, and then if they're on a course to achieve that, let it be as long as they fulfill their contract.

These are some big issues that make our field less efficient than it could be.

Continued >

Q **Dr. Opler: It's very interesting that you should share some of this with us. I've heard similar things, with a different emphasis, from some of your colleagues, both about the relative merits-or lack of merits-of competitive enrollment, as well as the lack of clinically informed trial designs; there's a growing consensus on this viewpoint. Going from there I think we're all getting a better sense of what we need to do better as a field. What areas do you that we need to focus on? Where are the opportunities in psychopharmacology?**

A **Dr. Liebowitz**: Well, I'm very excited about the whole issue of neurosteroids, for several reasons.

One is the staging program with Allopregnanolone. It appears that some of its success is that the treatment may actually be linked to some of the mechanisms of the disorders themselves. That is, there are these dramatic fluctuations in pregnenolone levels, rising through pregnancy and falling off; certain people are especially vulnerable to that. Actually treating with that substance–intellectually, that's a breakthrough in psychiatry in a variety of ways, both theoretical and clinical.

I think we'll see a lot more about neurosteroids going forward. It's very exciting: Some of these have novel mechanisms that we don't fully understand. I've been working for several years with Ferring Pharmaceuticals, which has some synthetic neurosteroids that in early trials seemed useful as a rapidly acting treatment for anxiety and depression. One of them, PH94B, just got picked up by VistaGen® Therapeutics to run its phase 3 trial for social anxiety disorder.

I also see big opportunities in the area of bipolar disorder. Our treatments of bipolar disorder are evolving to some degree, but more is needed. It's tremendously debilitating. With rapid psych mutations, we don't distinguish enough between bipolar 1 and bipolar 2. And when we do, we focus almost exclusively on bipolar 1 with severe mania and severe depression. Whereas, the bipolar 2s have mild manias, but more prolonged debilitating depressions. There are very few studies on bipolar 2 disorder, but it's very common. We exclude probably 20, 30 percent of the people that come to depression trials because they have some form of bipolar 2 disorder.

I would love to see studies on this, but we need different methodologies, because it's not just acute episodes: You really need to look at long-term stabilization.

Interestingly, we did something like that back in the 1970s. The patients would be seen every month and we could rate them on a seven-point scale. Four was euphonic and 3.5 was a little depressed, 4.5 was a little high. I don't really think our rating scales are sophisticated enough to capture that.

Continued >

Q

Dr. Opler: I'm very interested in your thoughts as an expert in this area: Do our current rating scales meet the challenge of the new mechanisms, the new pathways that we're persuing?

A

Dr. Liebowitz: Well I think you have to go disorder by disorder. It depends on your goals. If you're looking for gross-deviation psychopathology, it's pretty good–psychotic episodes, really shifts in severe depression, shifts in severe anxiety, things like that.

But what if you're looking for finer gradience? For example, in one of the studies we did with this neurosteroid for social anxiety, we had people rate day by day–or actually, exposure by exposure–how they were doing and whether it helped in comparing drug versus placebo. What we saw at the end of the week was a cumulative measure; it wasn't a fine-grain measure. We had to improvise and try to use a self-rating scale that allowed people to rate the severity on a one to 100 scale. So, I think for finer analyses and more subtle kind of things, we do need more scale development.

Q

Dr. Opler: I completely agree. Thank you for that insight. Now, let's talk about what is coming. What do we have to look forward in 2019?

A

Dr. Liebowitz: Well, I've got a lot to look forward to in the field. I'm very excited. We talked about the fact that we'd be doing more of these novel neurosteroid studies. We're about to begin a new Otsuka trial in adult ADHD with Centanafadine; that's an exciting development. I'm very interested in adult ADHD. It reminds me of where social anxiety was 15, 20 years ago. There's a huge reservoir of untreated people–especially of untreated adults or poorly treated adults or adults that were once treated. We have the stimulants, but we're looking for other drugs as well.

Adult ADHD causes a lot of disability, a lot of problems. And it intersects conditions as well; you get into a lot of comorbidity with anxiety disorders, depression, substance abuse, conduct disorder, all kinds of things. We'll just be getting started with it, but I'm excited about the adult ADHD programs coming along.

Of course, the read-out of some of the treatment-resistant depression studies will be coming–more with Janssen and the Rapastinel trials. We'll learn more about those. Those look like very important and exciting trials–again, rapid onset with novel mechanisms.

Continued >

Sunovion's binge-eating disorder study is very important and I'd like to see more data. There are some interesting patients because we don't see a lot of comorbidity there. But people are very distressed over their eating problems. So, those are just some of the things that I'm looking forward to.

Q

Dr. Opler: Thank you very much for that. I appreciate your sense of optimism. We have a lot to look forward to. Do you have any final thoughts?

A

Dr. Liebowitz: I think that we're seeing a growing sense of partnership in the field between sponsors, and CROs, and sites, and academic sites, and companies like MedAvante-ProPhase. I think we're working more collaboratively because of a growing understanding that we have a common interest in the field doing well. We all benefit, and certainly our patients benefit. It's something I'm very excited about.

Interviewee

Dr. Michael Liebowitz is a Professor of Clinical Psychiatry at Columbia University and Founder of the Anxiety Disorders Clinic — the first of its kind — at the New York State Psychiatric Institute. An internationally recognized expert and pioneer in Social Anxiety Disorders (SAD), Dr. Liebowitz created the LSAS, which is now a widely used primary outcome measure in clinical research on SAD. Board-certified in Psychiatry and Neurology, he has devoted over 30 years to the research and treatment of anxiety, phobic, and affective disorders, making major contributions in the areas of social anxiety, obsessive-compulsive disorder, panic disorder, atypical depression and rapid-cycling mood disorders.

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.