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Advancing Schizophrenia Care: Challenges and Promising New Therapies

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Andrew Cutler to discuss challenges in treating schizophrenia. Dr. Cutler is a Clinical Associate Professor of Psychiatry at SUNY Upstate Medical University, and he's also the Chief Medical Officer of the Neuroscience Education Institute in Carlsbad, California. Dr. Cutler, welcome to the program.

Dr. Cutler:
Thanks so much, Charles. It's a pleasure to be here.

Dr. Turck:
Well, to start us off, Dr. Cutler, what are some of the most common challenges associated with treating patients with schizophrenia?

Dr. Cutler:
Well, Charles, I hate to say it, but there are many challenges. The illness itself is a really devastating illness that starts early in life, and we're talking about people in their late teens, early 20s, when they're really developing and just starting to learn how to gain independence, social skills, and academic and work skills. And one of the big problems is there is a prodrome before the full-blown psychotic illness starts, and this prodrome is people start to withdraw, they look a little strange, and they seem depressed, but the problem is there's nothing about it that's specific enough to make that diagnosis.

Now, once somebody does develop this illness, it can be difficult to treat, and for about 70 years, we've had basically one mechanism of treating the illness, which is using medications that block a dopamine receptor—D2 blockers. The problem is they don't work for everybody. They work especially well for a subset of symptoms but not all the symptoms, and they can be associated with some real risks, including weight gain and metabolic disturbances, movement disorders, and endocrine abnormalities like prolactinemia. And what we've been learning about this illness is, independent of medicine, it's associated with significant medical comorbidities, including obesity, cardiovascular disease, and diabetes, and so we don't want to add to that with this.

Now, other challenges include the fact that the illness is affecting parts of the brain that have to do with self-observation, insight, and judgment, so very often people don't realize there's a problem. They don't think they're ill or that they need to take treatment, so adherence becomes a significant challenge with this illness. We know that if people take the medicine and continue to take it, they can have better outcomes, and we can cut down the risk of these devastating psychotic relapses. We believe, to be honest, you can even preserve brain tissue because, if untreated, this is a neurodegenerative illness where you can really see shrinkage and damage to the brain.

Now, once people, hopefully, do recover to some degree, then you have the challenge of picking back up with learning the life skills that were interrupted when the illness began. And so now there's real challenges with housing, with academics, with occupation, with relationships, and with being basically self-sufficient and independent. So that's just a partial list of the many challenges that we face.

Dr. Turck:
And how does the variability in schizophrenia symptoms play a role in treatment difficulties?

Dr. Cutler:
Yeah, that's a good point. I have been saying for a while this is a heterogeneous illness, and to be honest, I'm not calling it schizophrenia. I like to call it the schizophrenias because there are probably many different pathologies here. So, first of all, we know it's

heterogeneous clinically in the way it presents. Classically, we have four clusters of symptoms. We have the positive symptoms of schizophrenia, which people think of when they think of psychosis. These are hallucinations, delusions, and disorganized thoughts. We have the negative symptoms of schizophrenia, which are very devastating because the person withdraws. They don't have motivation. They don't speak a lot. They don't express emotion. And this can be very troubling for families when they see their family member just suddenly fading away and disappearing. Then we have the cognitive impairment, and this is probably the category that most interferes with function because these people have trouble being able to function independently, to manage the daily life skills we all do, to achieve and maintain a career, and so on. And finally, there are mood symptoms; depression, mania, things like that, anxiety. So it's been a challenge to find medications that work across this range of symptoms. And we know that some people present with more or less one of these groups of symptoms. There's not one classic presentation or fingerprint, and so the challenge has been, as I've said, having basically very similar mechanism drugs that work especially well for the positive symptoms but not as well for negative and cognitive impairment.

And finally, recently, we've had a newer mechanism, a newer medication approved, and the exciting thing here is that because these are probably different neurobiologic illnesses, heterogeneous neurobiologically and clinically, maybe there's a group of patients who might do well with a different kind of mechanism, and maybe a different mechanism might even help with a broader range of these symptoms.

Dr. Turck:
Now, looking at things from a different angle, how does the stigma surrounding schizophrenia affect patient outcomes?

Dr. Cutler:
Well, I wish I had better news. I have somewhat good news in this area, and that is there is a significant stigma associated with all psychiatric illnesses that I work with, of course. I think schizophrenia has been particularly stigmatized because these people look strange. They look odd. They stand out. Unfortunately, if not treated, they can even be so paranoid that they can be violent or aggressive; although the vast majority of patients are not, and they're more likely to be a victim of violence than a perpetrator of violence. But because of some high-profile cases and a real misunderstanding, because we're talking about disturbances of thought and emotion and to some degree behavior—we're not talking about something that looks as medical as, say, chest pain or shortness of breath, if you will—I think there's been a lot of misunderstanding. But we've made a lot of advances in understanding the biology and realizing that this is a real brain illness—this is not something somebody is under their control or just trying to be funny or whatever the stigma was.

I think also in recent years we've really done a good job battling stigma in general with mental illness. Certainly, there's been an epidemic of depression and anxiety in our country, and there's been a lot of focus especially on younger people and older people really with mental illnesses, so I think we've come a long way. I think that the stigma issue is better. But some of it also is culturally bound, to be honest. In some cultures, mental illness is less well-accepted than others, and that can really affect whether somebody with a serious illness like schizophrenia—whether they get treatment, whether their family recognizes the problem early enough to really institute effective treatment, so stigma can really get in the way.

Now, another way, there is institutional and systemic stigma, I hate to say. Mental illnesses for a long time were not covered to the same degree as physical illnesses, if you will, so there were inequities in our payment system, our insurance system. And, unfortunately, in our treatment system, often mental illness has been treated in separate facilities, sometimes community mental health centers, not part of a regular medical center or hospital, and they may not be as well funded, frankly. So there are all kinds of ways that stigma can permeate the recognition and the treatment of this condition.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Andrew Cutler about the challenges of treating schizophrenia.

Well, now that we have some background on treatment difficulties, let's dive into a roundtable discussion in which you participated and which was published in the *International Journal of Neuropsychopharmacology.* Would you tell us about the promising treatments you discussed?

Dr. Cutler:
I'm really happy to. As I said, this is a very exciting time, and really, we have entered what I now call the third wave of psychopharmacology. So the first wave started in the 1950s. And when you're talking about schizophrenia, there was a category of drugs there that were discovered to help the positive symptoms of schizophrenia, and what was found was this class of drugs was blocking a specific dopamine receptor called the D2 receptor. And so throughout the '50s and '60s and '70s and '80s, we had a number of newer drugs that were different kinds of refinements but all essentially had that same mechanism, and this led to a theory of

schizophrenia called the dopamine theory of schizophrenia. It was found there was too much dopamine being produced and released in the limbic system, the part of the brain that has to do with emotions and thoughts and behaviors, and not enough dopamine in the higher-level front part of the brain, which has to do with cognition and motivation and emotional expression. So it was this funny thing where now we are treating part of the illness with our D2 blocker, but we're not necessarily helping the other part of the illness.

Now, this was terrific for the fact that we could actually now start treating a lot of people, and some people got better, and some of them were able to get out of hospitals and things like that, but these medications were also associated with some significant challenges, including movement disorders—we call them EPS, extrapyramidal symptoms, Parkinsonism, akathisia—and a long-term side effect called tardive dyskinesia that a certain percentage of patients got, perhaps as many as 30 percent on the older drugs, which can be a permanent movement disorder that can be really disfiguring.

Then when I entered the field was the second wave of pharmacology. This is the late '80s, early '90s when we got a new class of drugs we called the atypical antipsychotics. They added affinity for a particular serotonin receptor and the D2 receptor, and by doing that they were called atypical because they decreased the risk of these movement disorders in particular, and that was a big step forward. We also hoped that by using these different receptors maybe we would help with some of the cognitive impairment and negative symptoms that are not touched by D2 blockade alone, and in some patients they did get a little bit better, but it was not as universally effective, I would say. Now, they were safer, and the second wave was kind of a revolution of safety. It was also, if you remember, the decade of the brain. There was a lot of money invested in research. It was a very exciting time. But these medicines were also found to have a significant risk of weight gain and metabolic disturbance, and as I mentioned, that's already an issue with these patients independent of medication, so we had to make these tradeoffs and these choices about benefit versus risk and so on. And, of course, you have to always remember there's a significant risk of inadequately treating the illness, right? These illnesses are devastating. It's a huge burden on families and society, so it is really important to find effective treatments.

Anyway, flash forward to now. As we've learned a lot more about the neurobiology, studying the brain is difficult. It's encased in a skull. The things that are happening are on a metabolic level. It's different from the heart. I can do an echocardiogram and see the heart doing its job pumping. I can do an EKG and see the electrical conduction of the heart. The brain is much harder to study, so it's only been more recently as we've developed more advanced tools that we can understand how the brain works better, and this leads to, perhaps, better and safer and more effective treatments. And on September 26, something really big happened in our field. A new medicine that represents a whole new class, a whole new mechanism, was FDA approved, and this medication is working through not dopamine directly—it's not binding those D2 receptors—it's working through muscarinic acetylcholine receptors. It turns out we've learned that acetylcholine has a strong relationship with dopamine, and if you lower acetylcholine, you can lower dopamine. But instead of blocking these D2 receptors which are found all over the brain—you're going to get a lot of collateral damage, I call it, because of blocking these receptors—these muscarinic receptors specifically M1 and M4, are located exactly where we want but not where we don't, so it allows for much more targeted treatment, effective treatment, without a lot of the collateral damage. So it is really the dawn of a whole new era. It's very exciting. It's leading the way here for maybe some other new discoveries. And again, it's only good for our patients to have more options.

Dr. Turck:
Do you have any other thoughts about how current research trends are influencing the future therapeutic landscape for schizophrenia?

Dr. Cutler:
Well, some things we need to learn are about this newer class in particular because there's actually now several of these medicines in development, so I think we're seeing a new generation, these muscarinic agonist medicines. And what we have to learn is what exactly they work for and what kind of patients they work best with. As I mentioned, the positive symptoms have always been the gold standard, treating those positive symptoms, and so the way these drugs are evaluated are basically based on the positive symptoms. That's what our rating scales are mostly focusing on. And yet there is some preliminary evidence that this mechanism may also help with those cognitive symptoms and negative symptoms that I mentioned earlier that are so impairing, especially impairing, and even more correlated with functional impairment, so there's some preliminary evidence they may help with those symptoms as well. As a matter of fact, the medicine that was just approved in a sub-analysis of patients who had particular cognitive impairment, their cognition improved quite significantly, so this would be very exciting to be able to have treatments that work not just on those positive symptoms but the whole range of symptoms because this is how we can get people to improve their function and quality of life, which is always the goal of really any medical treatment.

Dr. Turck:
Now, before we close, Dr. Cutler, is there anything else you'd like to share with our audience today?

Dr. Cutler:

Well, I definitely want you to be optimistic. Sometimes it has been frustrating. I know when I'm in the trenches working with people with schizophrenia, it's a very frustrating illness to deal with for us, for our staff, for our families, caregivers, treatment team. I want you to have a sense of optimism that there now are newer treatments.

One last thing. I didn't mention the category of drugs we call LAIs, which is long-acting injectable antipsychotics. This is also very exciting because, as I mentioned, adherence is a significant problem. And even patients who don't completely stop their medicine, if they take them inconsistently, it can be just as bad. You're still vulnerable to relapse. So one way to deal with this is a long-acting injection that keeps the blood level and the level in the brain therapeutic and consistent.

Now, up until now we've had a limited number of options of medicines available as an LAI because you have to have a certain chemical structure to lend itself to being an LAI. We have several new drugs in development that, again, is only to the good because it gives us more options. So I think the combination of new mechanisms, new formulations, new delivery systems is very exciting, and I'd like to end really with a message of hope that we can do better for our patients and their families.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Andrew Cutler, for joining me to discuss the challenges of treating schizophrenia. Dr. Cutler, it was great having you on the program.

Dr. Cutler:
Thanks so much, Charles.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.