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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Advancing Schizophrenia Care: When and How to Use Novel Therapies in Complex Patients

Announcer:
You're listening to *NeuroFrontiers* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *NeuroFrontiers* on ReachMD, and I'm Dr. Charles Turck. Here with me today to explore when and how we can use novel therapies in complex patients with schizophrenia are Dr. Ragy Girgis and Ms. Desiree Matthews. Dr. Girgis is a Professor of Clinical Psychiatry at the Columbia University Department of Psychiatry and New York State Psychiatric Institute, where he's also the Director of the Center of Prevention and Evaluation. Dr. Girgis, welcome to the program.

Dr. Girgis:
Thanks for having me, Dr. Turck. It's great to be here.

Dr. Turck:
And Ms. Matthews is a board-certified psychiatric nurse practitioner and the Clinical Director of Different MHP in Charlotte, North Carolina. Ms. Matthews, it's great to have you with us as well.

Ms. Matthews:
Oh, wonderful to be here.

Dr. Turck:
Well, let's start by grounding our conversation in the real world. Ms. Matthews, would you share a recent or memorable case where a patient didn't fully respond to conventional dopamine-2, or D2, receptor targeting agents?

Ms. Matthews:
Absolutely. I have a client that I'm currently working with. He's 35 years old. He's single. He's living with a diagnosis of schizophrenia, and he's been followed previously by a colleague and now myself in my outpatient practice.

Unfortunately, despite years of adherence to multiple antipsychotic regimens, he continued to experience breakthrough psychotic episodes characterized mainly by paranoia and intermittent auditory hallucinations. But even during periods when his positive symptoms were well controlled, he was still left feeling—and these are his words—"drugged" and "zombie-like." And that really reflected some significant, unresolved negative symptoms.

So he had gone through a well thought-out treatment plan, but we saw problems with efficacy and tolerability. When he saw me after his last failed treatment—and this was, again, due to positive symptoms breaking through and inability to increase the dose any further—he told me, "Desiree, I'm just not taking antipsychotics anymore." He told me he was going to just live with the symptoms because another medication trial was just too much for him to bear. He really wanted to regain motivation. He wanted to leave the house again. He wanted friendships and social connections. He wanted to feel healthy and maintain his recent weight loss. So he really felt very hopeless about another trial of an antipsychotic.

So when considering newer approaches to the treatment of schizophrenia, historically, we've relied on these D2 binding approaches or a modulation with our treatments. So when I consider new mechanisms, such as the muscarinic modulators—in this case, muscarinic agonists—I approach this in terms of clinical practice: thinking about the need for both efficacy and tolerability. Both of these factors play

a major role in my decision to initiate or switch treatments.

Unfortunately, many patients either do not achieve adequate symptom relief with traditional D2 binding treatments like antipsychotics, or they may experience adverse effects that can limit adherence and continuation. In those situations, a therapy that works through an alternative mechanism may be ideal, such as these muscarinic receptor modulators, and they become an important part of my clinical decision-making.

When we think about this, it really offers a completely different pharmacological pathway, which can be really valuable when a patient has had, say, repeated trials of D2-blocking agents that have either provided insufficient benefit or burdensome side effects like weight gain, sexual dysfunction, or drug-induced movement disorders. Muscarinic modulators don't bind to D2 directly, so they can potentially help me reduce the core symptoms of schizophrenia without adding to the cumulative D2 blocking-related risks.

So this illustrates, I think, many of the challenges that we see in clinical practice: having to weigh the efficacy versus the side effects and the tolerability. But also, sometimes our treatments really overlook the negative and cognitive symptoms. We don't really necessarily have a silver bullet to target that. So this really highlights why clinicians and patients may seek alternative mechanisms beyond those traditional D2 antagonists.

When I talk to patients about the fact that they have another option now that's not classified as an antipsychotic, patients and families are really interested and excited, in many cases, that they have another option. You know, the term “antipsychotics” still carries a lot of stigma, and patients frequently associate these D2-binding treatments with side effects like weight gain, sexual side effects, and movement disorders. So framing muscarinic modulation as a different therapeutic pathway—one without this direct D2 blockade—really can help patients start treatment and alleviate some of the worries that they've experienced with treatment in the past. Unfortunately, many of my patients have gone through cycles of D2-binding treatment, whether that be problems with efficacy, side effects, or both. But patients and families alike have actually been really excited that we can offer a treatment that's not considered an antipsychotic.

Dr. Turck:
Thank you so much for sharing that case with us, Ms. Matthews. And if we turn to you now, Dr. Girgis, what clues or patient characteristics signal to you that it might be time to explore using a medication with a novel mechanism of action?

Dr. Girgis:
Yeah, this is an important question. A lot of the challenges confronted by patients, families, and clinicians were brought up by Ms. Matthews, and they’re very universal. There are several ways one could look at this. So on the one hand, there is very much a categorical distinction between what medications work, especially in terms of efficacy for schizophrenia, and what don't. And those are, of course, the dopamine receptor blockers, and even medications like xanomeline, which are muscarinic agonists, probably work by antagonizing dopamine. So all the medications probably antagonize dopamine or decrease dopaminergic function or whatever.

And then you have to look at safety. On the safety side of things, there's much more of a spectrum of effects, which is almost definitely related to the different mechanisms of action of all the different antipsychotic medications, from the very potent dopamine-2 receptor antagonists—what we call the first generation or typical antipsychotic agents, like haloperidol, to the partial agonists, which cause very few extrapyramidal side effects, such as aripiprazole and brexpiprazole, and even cariprazine, which is actually quite different because it's the only antipsychotic medication that is dopamine-3-preferring. And now xanomeline, which doesn't touch dopamine receptors at all, has essentially no EPS liability. And then everything in between. So it's really maybe more on the side effect side of things that we pay more attention to than the pharmacological profile and those sorts of things.

So in practice, what does that mean? In practice, while in terms of efficacy, there are really no data to suggest that one unique mechanism of action, among those that we discussed, will work better than another. On the side effect side of things, there's probably substantial evidence to suggest that one would react differently to these sorts of medications. And everyone reacts, as we all know, differently to different medications with some similarities. But for example, if one experiences lots of weight gain with a relatively low potency agent, such as a clozapine, olanzapine, quetiapine, or something like that, it would be reasonable to next try something like a high potency dopamine-2 receptor antagonist, one of the partial agonists, or xanomeline, and vice versa.

But that's how we think about how to mix and match medications with individuals. And again, everything is always very individual and depends a lot on a person's preferences, history taking medications, what they want, what their goals are, and everything in between those things.

Dr. Turck:
So once you've identified some of the challenges we've been discussing, Ms. Matthews, how do you integrate these novel therapies into care plans, especially when weighing factors like patient goals, family support, and history of patient adherence?

Ms. Matthews:
Typically, I use a cross-tapering strategy. So if they are continuing to be adherent to their D2-blocking antipsychotic, usually I will cross-taper and start the new agent while I slowly decrease the original medication. Of course, we have to ensure there's no significant drug interactions. Is this emergent that we really need to get them off quickly? So it really is very individualized.

If you look in the prescribing information for these medications, unfortunately, there's not a go-to written ledger where we decrease, so we really have to use our clinical decision-making as well as making sure that the cross-titration is something that the client is able to adhere to.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontier*s on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Ragy Girgis and Ms. Desiree Matthews about best practices in managing complex cases in schizophrenia care.

Now, coming back to you, Dr. Girgis, what role does the multidisciplinary team play in helping you navigate difficult treatment decisions in caring for patients who have schizophrenia?

Dr. Girgis:
They play the most important role, and I would include family in that. The medications themselves are very important, of course. Their pharmacological profilers are extremely important, and we need to know about those and think about those and all of that's important. But what's more important is everything else. And we can describe that as psychodynamics, transference, countertransference, therapeutic alliance, and relationships. All of that is so much more important because ultimately, the patients need to trust providers and the medications. They need to have patience. They need to feel that they can communicate how they're feeling with their providers and those sorts of people. They need to have confidence in whatever plan they may have. And a lot of the time, especially in our population who tend to have somewhat challenged insight with regards to some of their symptoms and conditions, that is all the more important. And again, I'm definitely including families.

So while there are prescribers and providers who prescribe medications, we are actually probably one of the less important components of the multidisciplinary team. The social workers, the nurses, the case workers, and most importantly, the family or close acquaintances are almost always more important. They spend more time with patients. They process how patients are feeling in most cases, except in those few cases when a prescriber is also administering therapy and those sorts of things. But in almost all cases, these people are working with the patients to a much greater degree—helping them to adhere to medications, encouraging them to not just try medications, but again, communicate with the prescribers about how they're feeling, and also providing psychoeducation about their condition and medications. All of this is very important.

Dr. Turck:
Now, some patients may be hesitant and even fearful when they hear the phrase “new medication.” So before we close, Ms. Matthews, what messaging seems to resonate best when broaching this topic with patients based on your experience?

Ms. Matthews:
Absolutely. Starting a new medication is never easy. Remember, many of these individuals have tried multiple different treatments, whether that's in the hospital or in the outpatient setting. So when I introduce a new medication option for individuals, I really start by validating the patient's past experiences. So if they've struggled with side effects or felt let down by prior treatments due to efficacy, I acknowledge that frustration and make it clear that we are hopefully not repeating the same approach; we're trying something that works differently and we go step by step together with close follow-up, and that can really help build trust.

I also ask clients about their deal-breaker side effects—things that they feel like they cannot live with, even if a medication is effective. So if I know we may want to avoid metabolic effects, such as weight gain, or maybe we want to avoid things like drug-induced Parkinsonism, that may steer me to one treatment or another.

And certainly, always address the stigma. Sometimes people feel that they are the failure, so I let patients know that needing another option doesn't mean that you've failed; it just means that this medicine is just not the right fit for you. So frame that conversation to shift it from people blaming or feeling hopeless to more of a problem-solving one. And I feel like this really resonates with the patient and leaves them feeling empowered rather than discouraged about, “oh, another medication trial.”

Dr. Turck:
Well, with those key reflections and strategies in mind, I want to thank my guests, Dr. Ragy Girgis and Ms. Desiree Matthews, for joining me to share their approaches to managing complex patients with schizophrenia. Dr. Girgis, Ms. Matthews, it was great having you both on the program.

Dr. Girgis:
Thanks, Dr. Turck. It was a pleasure to be here.

Ms. Matthews:
Thank you all. It was wonderful to be here.

Announcer:
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