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Rethinking Schizophrenia Guidelines: Why It's Time to Incorporate Novel Mechanisms

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:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the need for updated schizophrenia treatment guidelines that incorporate novel drug classes is Ms. Desiree Matthews, who's a board-certified psychiatric nurse practitioner and the Clinical Director of Different MHP in Charlotte, North Carolina. Ms. Matthews, thanks for being here today.

Ms. Matthews:
Oh, thank you for having me. I'm really looking forward to this discussion today.

Dr. Turck:
Well, to help set the stage for our discussion. I'd like to frame a parallel for us. If we look at treatment guidelines in the area of, say, cardiology, they've evolved over the years to become a layered, mechanism-driven roadmap that includes a variety of therapeutic classes. Schizophrenia guidelines, on the other hand, have remained static and continue to be largely centered around dopamine receptor 2, or D2, antagonism. So with that in mind, Ms. Matthews, why might this comparison to cardiology care be useful when thinking about the future of schizophrenia care?

Ms. Matthews:
I love that parallel, and I think if we narrow it down to the treatment, say, of hypertension, it's really evolved over the years to become layered in terms of a mechanism-driven approach roadmap that includes a variety of therapeutic classes. As you mentioned with schizophrenia, by contrast, it has remained absolutely fairly static. For decades, we've really relied upon entirely a D2 receptor antagonism-driven model. So while these medications have been life-saving for many, there's still many patients that could potentially do better, whether that's overall efficacy, side effect burden, as well as tolerability.

So comparing that to hypertension treatment is really useful if you think about their advancements. They didn't just abandon the older therapies; they've really layered it with new mechanisms. And psychiatry is maybe reaching that same point with schizophrenia. So I think the schizophrenia guidelines can absolutely mirror the same evolution that we saw with hypertension.

Dr. Turck:
Now, as I alluded to earlier, current schizophrenia guidelines are still structured around the typical versus atypical distinction, prioritizing D2 blockade and tolerability rather than mechanism of action. Now, from your perspective, how does that framework present limitations in day-to-day practice?

Ms. Matthews:
If you look at the neuroscience-based nomenclature, otherwise known as NBN, this has really been a growing movement to rethink how we classify and name these medications and try to shift the focus from what they treat, like antipsychotics treating psychosis. Shifting from a disease to mechanism-based nomenclature can really reflect our science and the research that has been done in neuroscience.

So within this framework, agents considered traditionally atypical antipsychotics may be better conceptualized by calling them serotonin dopamine antagonists or partial agonists. And by viewing the medications like this, it may help align mechanism with potential patient-specific needs.

So in practice, by viewing these medications as typical versus atypical, we can see them almost as interchangeable. And now, of course, with the advent of novel mechanisms of action, such as our muscarinic receptor agonist—and we do have one that is currently FDA approved, xanomeline and trospium chloride combination for the treatment of schizophrenia—this really challenges our notion of, what do we call these other treatments? So I absolutely think names matter, and they may allow for a more nuanced discussion and implementation into clinical practice.

Dr. Turck:
Well, given some of the limitations we've been discussing, and you've mentioned a little bit about this already, there is good news in that several novel agents that operate outside the traditional D2 model are now available or in development. So how do these newer mechanisms challenge the way current guidelines are organized?

Ms. Matthews:
Even within classes, efficacy doesn't change too much outside of, of course, clozapine for treatment-resistant schizophrenia. But if you really drill down and take a look at side effect profile and tolerability, that's really where you're going to see a lot of differences within those classes. And this really challenges our view that we need this 80 percent threshold of D2 blockade for efficacy, yet we see fairly robust symptom control and really good tolerability for the most part in the clinical trials for schizophrenia. So we really can't make sweeping conclusions about a type of medication just based on our current nomenclature and how we classify treatment.

But without clear guidelines, it could be difficult to figure out, okay, what do I use, and when do I use it? How do we switch, and how do we incorporate even more recent novel advances, such as xanomeline trospium chloride? This represents a completely distinct mechanism—reducing dopamine pre-synaptically rather than blocking D2 post-synaptically.

So I really think highlighting the mechanism but also looking at the tolerability and safety profile within the guidelines that may be developed in the future could give us a little bit more in terms of clinical practicality.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Ms. Desiree Matthews about why and how schizophrenia treatment guidelines need to be updated.

Now, if we continue examining the current guidelines, Ms. Matthews, another gap is around safety monitoring and real-world implementation. The novel antipsychotics I had mentioned earlier and that you'd discussed earlier may have unique side effects or drug interactions, but current guidelines don't offer much beyond phase 3 trial data, which usually lack head-to-head comparators. So what would be more useful guidance, and what would that look like for clinicians navigating these complexities in practice?

Ms. Matthews:
I think a common question that we get is, how do we actually use a new novel agent, especially considering that many of our clients in the real world are not clinical trial patients? Meaning, in the real world, we're treating people with multiple medical and psychiatric comorbidities, polypharmacy, and variable adherence that's really washed out and excluded from clinical trials for good reasons. But still, clinical trials may not always reflect the level of complexity that we see in our own clinical practice.

So just thinking about navigating new agents, I really want to know, how do I monitor our patients? What do we need to look out for in terms of most common side effects? And can I manage some of those side effects? What are some drug-to-drug interactions? What about dose adjustments, especially for people that may be medically complex? And I think one of the biggest questions we face as clinicians is really when and how to switch. So when I switch from, say, an atypical antipsychotic to a new novel treatment, what does that look like? How do I cross-taper? Are there any directions?

So I think navigating that with new treatments is probably one of the biggest challenges that we have in clinical practice. Switching data and adjunct treatment data past phase 3 clinical trials—really incorporating more of these real-world conundrums could help us guide

our clinical practice.

Dr. Turck:
And if we look beyond medications for a moment, today's guidelines also tend to focus on symptom severity scales, but they don't always take into account functional outcomes like motivation, affective flattening, or cognition. So with that being said, how important is it for updated guidelines to help us match treatments to functional domains rather than just symptoms?

Ms. Matthews:
That's a great point-out. When we look at our current framework guidelines and assessment tools, it still focuses on symptom reduction. In fact, in clinical practice, there is not, I would say, a great, easy, or quick tool to measure certain symptoms of schizophrenia. And with schizophrenia, we know this is a syndromal disorder. It's not just about psychosis. A lot of times, we see a patient being stable on paper—they don't have any hallucinations, there's no acute agitation, and they're not going to the hospital—but they still struggle with things like motivation, affective flattening, cognitive impairment, and engaging socially. We also see a lot of negative and cognitive impairment that may not be truly resolved with current treatments, unfortunately, but these are often true detriments to day-to-day functioning and quality of life.

So for that reason, we really do need to look at rating scales to help us potentially match treatments to functional domains and not just symptom clusters. Incorporating patient-reported outcomes and real-world functioning metrics in clinical trials could help us with consideration of treatments. But ultimately, our goal is not just to reduce psychosis; it's actually to help patients rebuild their lives and really thrive despite the illness. And unfortunately, I don't think we have guidelines that come right out and say it. But absolutely, I think a rating scale could help us in clinical practice be more attuned to patient-reported preferences, outcomes, and their true functional status.

Dr. Turck:
Now, we're almost out of time for today, but if we look ahead before we close, Ms. Matthews, what else would a next-generation schizophrenia guideline need to include to be truly useful for both clinicians and patients?

Ms. Matthews:
Yeah, absolutely. So if I could choose the framework for the next-generation schizophrenia guideline, I think it's a big undertaking, but I think we can do it. We really need to move beyond this D2 centric, D2 blockade legacy framework that we've had for decades and now consider adding in those current novel treatments. So I think we should be looking more at the mechanistic diversity that we have within our treatments for schizophrenia.

But also, I think it needs to reflect the realities of clinical practice—so addressing things like adherence challenges, promoting early and proactive discussions about LEIs, and providing guidance for negative and cognitive symptom predominance. And I think equally important is the focus on prevention, meaning preventing metabolic collateral effects before they occur rather than waiting to intervene once they develop. And I do believe that the recently published INTEGRATE International Guidelines for Schizophrenia has begun to address some of these gaps, but certainly we need to consider to move forward with incorporating those novel treatments.

Dr. Turck:
Well, as those forward-looking comments bring us to the end of today's program, I want to thank my guest, Ms. Desiree Matthews, for joining me to discuss the importance of updating the schizophrenia treatment guidelines to include novel drug classes that go beyond standard D2 antagonism. Ms. Matthews, it was great having you on the program.

Ms. Matthews:
Thank you for having me.

Announcer:
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