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Rethinking Schizophrenia Treatment Through Muscarinic Modulation

Announcer:
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Dr. Rubio:
Despite the recent approval of muscarinic therapies like xanomeline and trospium for the treatment of schizophrenia, many clinicians remain unfamiliar with how these drugs work, their clinical effectiveness and their safety profiles compared to traditional D2 receptor antagonists.

Welcome to our discussion aimed at helping you choose the right treatment for your patients. This is CE on ReachMD, and I am Jose Rubio. I am Assistant Professor of Psychiatry at the Zucker School of Medicine in New York, and with me is my colleague and friend, Dr. Jonathan Meyer.

Dr. Meyer:
Hi everyone. I'm Jonathan Meyer. I'm a voluntary Clinical Professor of Psychiatry University of California San Diego, and a Senior Academic Advisor to the California Department of State Hospitals.

Dr. Rubio:
Thank you very much, Jonathan, for joining us for this conversation. Let's talk about treating schizophrenia and choosing therapies. From your perspective, what are the differences between muscarinic and dopaminergic antipsychotics in terms of their mechanism of action, the efficacy, and side effect profile?

Dr. Meyer:
Well, I think mechanism is really the most important one in many ways, because we've come to appreciate that people who have schizophrenia, who aren't treatment resistant, have a dopamine problem. They produce too much dopamine presynaptically in a certain tract. We've been traditionally managing that with a nonselective postsynaptic solution. We give a D2 blocker, which does block dopamine where we want it to, but unfortunately, Jose, as you know, it goes to the motor area, the striatum, the pituitary, the pancreas, and gives us off-target effects.

The elegant aspect of muscarinic agonism is that it works presynaptically, where we always want it to work. It turns off the flow of dopamine. And what's really interesting is it does it selectively. It does it in the area of the striatum, where we have positive symptoms, and it largely spares the motor area, and it has no endocrine side effects either.

From that, we can see in the clinical studies that we don't see a signal for movement disorders, we don't see a signal for endocrine problems, we also don't see weight gain or other metabolic adverse effects. So it sounds very exciting.

The efficacy is not any different than agents we've had for a number of decades. There was a meta-analysis recently this past year by Fabiano, Christoph Correll and company, which computed the effect size using the meta-analysis method as 0.56, which is very much on par with the agents that we've had for a number of decades, like olanzapine and risperidone. So we can't say it's more effective, but certainly the adverse effect profile was very, very different.

There is one thing though, which I think we'll talk about in a second—while we don't get the D2-related adverse effects, Jose, what are the adverse effects that we do get from muscarinic agonism?

Dr. Rubio:
Well, there's all the procholinergic and anticholinergic side effects that doctors may not be so familiar with. This is a very different profile drug, right?

Dr. Meyer:
Absolutely. And when you say procholinergic, I think you might as well just say, what are the things people run into as they titrate the muscarinic agonist medications?

Dr. Rubio:
Well, the most common is going to be nausea, right? Also frequently you see patients experiencing even vomiting, constipation, diarrhea. These tend to be the most common side effects that patients tend to experience. Although, in my experience, and based on the data, seems that this is something that occurs during titration, not so much later in the treatment.

So this is probably something that doctors need to get familiarized with, because it's something that we are not so used to managing, right? Anticholinergic a little bit. We have antipsychotics that are highly anticholinergic, but given the combination of anticholinergic and procholinergic agent in the only approved muscarinic antipsychotic, it's a whole new situation that we're going to have to be educated on.

Dr. Meyer:
Yeah, and I agree. And as you say correctly, it is during the early titration. And the thing that really bothers patients the most are the procholinergic adverse effects—nausea and occasionally vomiting.

So there's a couple of strategies which you might as well just talk about now to manage this. One, of course, is make sure people take it correctly. One thing we know from the kinetics is that if trospium is taken with food, you lose 85 to 90% of that. And the purpose of trospium is to mitigate the procholinergic adverse effects of the xanomeline. You have to make sure people take xanomeline-trospium an hour before a meal, or at least two hours after, otherwise you lose your trospium, and then the patient is losing their protection for the procholinergic adverse effects. So that's one thing.

The other one is the titration. In the clinical trials, the titration was fairly aggressive, because these were people who were acute, exacerbated inpatients who you wanted to get better quickly.

And so, in addition to perhaps altering the titration, which may or may not be the way to go, there's a couple of other strategies. In the clinical trials, they used ondansetron, and you have to take it ahead of time, but this does help with nausea.

But there's another strategy which you could use, which is actually giving people extra trospium. Trospium is available in various strengths. And as long as I'm not too concerned about giving somebody, let's say, urinary retention—which is a real problem, by the way—that I may actually give them extra trospium. The lowest dose available is 20 mg. And if the person is so fearful of the nausea or vomiting, I will actually have them take extra trospium at the beginning. And then if the problem doesn't manifest itself, we can peel it away, but at least it gives me exactly what you're suggesting might be helpful, which is having more exposure to the agent which is mitigating those procholinergic adverse effects.

Eventually, people do develop tolerance—we know this from the clinical trials. The idea is you got to get them over the hump. And I think from the perspective of both of us who treat a lot of people living with schizophrenia, you've got to take the long view. If it takes you a month to get them to the effective dose, that's fine. If they can do it in a week, that's fine too. You have to treat the person in front of you based on their concerns.

Dr. Rubio:
For those tuning in, you're listening to CE on ReachMD. I am Dr. Jose Rubio, and here with me today is Dr. Jonathan Meyer. We are discussing schizophrenia treatment through muscarinic modulation.

Dr. Meyer:
So this is an exciting drug. So I guess the question Jose is, when would you switch somebody to xanomeline-trospium?

Dr. Rubio:
Yeah, that's a very interesting question. And obviously it's very important, right? Who are the right candidates for this drug? And the way I think about this is that I would divide it in two types of problems. One is when the antipsychotic has not been effective enough, and the other is when the antipsychotic might have been effective, but it's still causing some side effects that are difficult to tolerate.

So going to the first one, when the drug has not been sufficiently effective, I would look separately at positive symptoms, negative symptoms, and cognition. From the perspective of positive symptoms, I think that the data, first of all, we have to admit that there's no head-to-head comparison between the xanomeline and trospium and other drugs. So it's a little bit difficult to come up with very robust statements on this regard. But you see that in the ARISE trial, the use of the xanomeline in augmentation with other antipsychotics for the treatment of residual symptoms was not really reaching statistical significance, which makes me think that perhaps those residual symptom patients might not be the first place where I would start in the use of xanomeline for sufficient efficacy. Perhaps the indirect data that we have, as we alluded to, for negative symptoms and cognition, might be a place where I would consider it more seriously when it comes to insufficient response.

And then from the perspective of side effects, then I would go after those side effects that are so common, so pervasive with antipsychotics; those being weight gain, metabolic disturbance, motor side effects, tardive dyskinesia. The event of hyperprolactinemia. So that would be, to me, a target population, those that are experiencing any of the side effects that perhaps would benefit from having a drug that does not have that as a side effect.

Dr. Meyer:
Yeah, you and I both work with early phase people living with schizophrenia who are very sensitive to all sorts of adverse effects: motor, weight gain, endocrine. And to me, I think the advantages there are tremendous.

So this is sort of a monotherapy. But you mentioned the ARISE study, which is adjunct. And I think you already kind of tipped your hand there. The data weren't positive. They did the study. These are people with residual symptoms and the addition of xanomeline-trospium didn't generally make some people better, although there were some subgroup analyses which show there might be a benefit. Would you still consider it adjunctively in some cases before, let's say, going on to our favorite medication, which is clozapine?

Dr. Rubio:
Yeah. Well, if you ask people in the field, that's really how this drug is being used. Most often this drug is being used as polypharmacy, which is not the way the drug was studied in the pivotal trials. So I believe that most often this is either an adjunct to olanzapine or clozapine, if you ask people in the field. So it's a very different way of using it compared, again, to the studies.

Me, personally, I think that I would tend to use as monotherapy. There might be some cases in which—again, we are doing this without any good quality evidence—but there might be some cases in which, if there are some residual symptoms that—residual negative symptoms or cognition, you could use it as augmentation. But that's not really how the drug was studied. So you are on uncharted territories when you're doing that, however, that's what we are seeing in the field.

Dr. Meyer:
Yeah, I think—and certainly, there are some people who can only get so much D2 blockade in their system, and they're limited by that, and so the idea of working presynaptically may help them out, because they just have a lot of side effects from D2 blockade, which limits

their exposure.

But, if you're only going to switch somebody, let's say, from a D2 blocker to xanomeline-trospium, what are some pointers out there for folks?

Dr. Rubio:
Yeah, I think that that's an important question, right? So if you're going to do a switch and not an augmentation, I think augmentation, it also has its challenges, right, particularly if you're doing augmentation with a drug that's very anticholinergic, like clozapine or olanzapine, right? So I think if you're doing that augmentation to have on top of xanomeline, on top of a highly anticholinergic drug, you may want to be very cautious about the potential for a lot of anticholinergic side effects.

And perhaps that's a place to play with the dosage. Perhaps that's a case in which you may have to take it with food so that you don't absorb the trospium, because they already have on board high anticholinergic burden.

If you're doing a cross titration, you're changing the drug to something else, I think it is important to take into account what is the anticholinergic load that the patient is coming in with? It's not the same thing, say, that you're switching from risperidone to xanomeline, then from olanzapine to xanomeline. So I think that depending on what is the drug that I am using, that the patient is coming from, you may have to be more attentive to the procholinergic or anticholinergic and anticipate that you may have one or more of the other.

Typically, what we have been doing is to switch patients or to cross titrate over 4 weeks, although now I am of the perspective that probably a quicker cross titration might also be fine. What do you think about this?

Dr. Meyer:
I think the issue of current anticholinergic burden is an important one.

Dr. Rubio:
Well, this has been a fantastic conversation, Jonathan, but before we wrap up, do you want to share a take-home message that you would give to the audience?

Dr. Meyer:
As of now, we only have one muscarinic strategy for schizophrenia, and if there's going to be others they are going to be many years away, get comfortable in learning how to use this so your patients can get the benefits of everything we discussed—the absence of certain adverse effects, benefits not only in positive symptoms, but maybe other elements of schizophrenia. But in order for them to get the benefits, you have to know how to start it and how to manage some of its quirks.

Dr. Rubio:
I agree. I would highlight that this is a very new medication. The side effects, the titration, there are many aspects that are going to be new to most prescribers. And unfortunately, you could have bad experiences if you're not familiar with how to use this drug. And it would be unfortunate if a bad experience turns you off to something that actually could be very helpful.

So I fully agree with you, Jonathan, I think it's very important that people become familiar with how to use this drug, how to manage side effects, so that patients can get the benefit that this drug seems to have according to the data that we have and the data that is emerging.

And that's all the time we have today. So I want to thank our audience for listening in. And thank you, Jonathan, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Meyer:
My pleasure, Jose. And thank you all to the audience. I hope you found this interesting and informative, and I hope you all have a good day.

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