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Chairperson's Perspective: Incorporating Novel Treatment Options for Schizophrenia Into Clinical Practice - Overcoming Clinical Inertia

Opening:
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Dr. Rubio:
Hello, this is CE with GLC, and I am Dr. Jose Rubio. I am Assistant Professor of Psychiatry at the Donald and Barbara Zucker School of Medicine at Hofstra University and Institute of Behavioral Science, the Feinstein Institute for Medical Research, Northwell Health Division of Psychiatry Research, and the Zucker Hillside Hospital.

Today, I'll be highlighting the key messages presented at the satellite symposium by Total CME at a recent meeting in Miami, Florida.

So let's get started with some of the basic aspects of how antipsychotics work, at least the dopaminergic antipsychotics. Positive symptoms are the result, in part—at least, that's what we think—of an excess dopamine into the striatum. There are neurons that go from the midbrain to the striatum that produce too much dopamine in a way that is excessive constantly but not necessarily corresponding with a given stimuli.

So the antipsychotics work by blocking the effects of that dopamine release in the postsynaptic neuron. They block the D2 receptor postsynaptically, and that mitigates the response that you would get from the endogenous dopamine.

Now, there are several dopaminergic pathways in the brain, and all of the dopaminergic agents are going to block the D2 receptor everywhere in the brain. Some of this is going to be on target, some of this going to be off target. On target is the nigrostriatal pathway, so those are neurons that are hypothesized to be responsible for the positive symptoms. By blocking that circuit with the D2 blocking agents, you're going to mitigate psychotic symptoms, and that is the on-target effect.

But there are off-target effects of antipsychotics, the dopaminergic antipsychotics. These are, for instance, in the nigrostriatal pathway 2, which is the dorsal striatum. Those are neurons that code for motor information, so by blocking the D2 receptor there, you can have extrapyramidal side effects.

So these are all off-target effects that are undesirable, and that's why there is a whole pipeline that is currently underway in terms of drugs that can be developed to address the pathophysiology of schizophrenia in a way that's more selective and that causes less of this off-target effects.

Here you can see a depiction of the basic circuit of the upstream effects, if you will, or the upstream inputs of this dopaminergic neuron that we were saying that goes awry in schizophrenia. So you see this dopaminergic neuron receives inputs from cholinergic interneurons in the midbrain and also receives inputs from the cortex. These are glutamatergic neurons that project from the cortex to the midbrain. And so what you see is that the current armamentarium of therapies that we have for schizophrenia addresses the problem really downstream in that connection between the dopaminergic neuron and the medium spiny neuron.

And it does not address the really the upstream issues that we are hypothesizing occurring in schizophrenia, namely the aberrant firing of glutamatergic neurons in the cortex. This is known as an excitation inhibition imbalance. And what it means is that this glutamatergic cortical pyramidal neuron that projects into the midbrain should be controlled by this GABAergic interneuron. Right? So under normal circumstances, there should be a back and forth between the excitation of the glutamatergic neuron into the GABAergic neuron and the inhibition of the GABAergic interneuron into the glutamatergic neuron, so there should be an excitation inhibition cycle that should regulate the firing of the glutamatergic neuron. Now, we think that this is not functioning correctly in schizophrenia, and there's an excitation inhibition imbalance.

So you see here you have several agents that have been developed to target all of this cascade of events. Some of the agents are trying to reduce the amount of dopamine that is secreted by these dopaminergic neurons. That would be the case of the TAAR1 agonist.

Now, there are other agents that are mitigating the problem by reducing the inputs that this dopaminergic neuron receives, either by the cholinergic interneurons in the midbrain—that would be the M4 agonists—M4 receptors being mostly in the midbrain and subcortically. And then the muscarinic M1 receptor agents, that what they are going to do is that they stimulate the GABAergic interneuron, and they're going to increase the inhibition of this glutamatergic neuron that intrinsically is firing more than what it should, and therefore it's restoring the EI imbalance, the excitation inhibition imbalance, that you see in schizophrenia.

Now, to zoom in into what is the mechanism of action of this muscarinic agents, which, as I'm explaining, it's part of the armamentarium that is under development to address the pathophysiology of schizophrenia upstream from the dopaminergic dysfunction. The way it works, M1 is that the M1 are highly concentrated in the cortex, the M1 receptor, and they are densely located in the GABAergic interneurons. And the way it works is that by stimulating the M1 receptor, they are going to stimulate the brake, if you will, on this pyramidal neurons that are hyperactive, and therefore you're seeing an inhibition of the pyramidal neuron that projects into the midbrain, right? So that dopaminergic neuron that's in the midbrain is going to receive less of a stimuli. That is the M1 mechanism of action.

The M4 mechanism of action is subcortical, being M4 receptors located mostly in the subcortical areas, namely the ventral tegmental area and the striatum, nucleus accumbens, for instance. And what you see is that by operating on the M4 receptor, you're going to decrease the amount of acetylcholine that's released into the dopaminergic neuron, right? So that's going to decrease the amount of acetylcholine, which is exciting the resting action potential of these dopamine neurons. And in effect, what's going to do is that's going to reduce the amount of dopamine that these neurons are going to release into the striatum.

There are a number of drugs that have been developed that exploit either the M1 or M4 mechanism. The one that's in the market is xanomeline-trospium. There are several others on the way. Xanomeline-trospium is an M1 agonist, M4 positive allosteric modulator. It's given in combination with trospium, because xanomeline, being the active compound, is very difficult to tolerate because of the effects it has in the periphery. The procholinergic effects that it has on the periphery, therefore it has to be given in combination with an anticholinergic drug that doesn't cross the blood-brain barrier.

So this is the design of xanomeline-trospium, the registrational trials that were used to get this drug approved. And what you see is that there are several of them, they all have the same design. It's 50/20 mg of xanomeline-trospium, 50 mg xanomeline, 20 [mg] trospium, BID, or placebo. And then the patients were, if they were on the active compound, they were increased to 120 [mg] BID of XD, meaning 100 mg of xanomeline, 20 mg of trospium, BID. And then they were increased day 7, so day 8 and onward they are increased to 125/30 [mg]; 125 [mg] xanomeline, 30 [mg] trospium. So it’s that or placebo.

What you see is that in the acute trials EMERGENT-2 and EMERGENT-3, the results look almost identical. Same design, same inclusion criteria, some same study titration schedule, and you see that on week 2 there's a separation against placebo. So there's a separation that keeps growing, and at the endpoint at week 5 there's an effect size of 0.61 in EMERGENT-2 and same thing for EMERGENT-3. It's identical results. So this is a comparison against placebo. There's not a comparison head-to-head against another

drug, but this is comparable to the effect size that you would observe with a drug like risperidone, for instance.

So this was compelling enough for the FDA to grant the approval for the drug to go to market. There are additional pieces of data that supported this. So when patients were switched from, in the acute phase studies, from the placebo to the active compound, these patients improved, and there was a sustained improvement for an entire year. So it seems that the benefit is long-lived.

For those just tuning in, you're listening to CE with GLC. I am Jose Rubio, and we are discussing incorporating muscarinic agents into the treatment of schizophrenia.

There were additional pieces of information that were interesting from those registrational trials. Obviously, the endpoint was total symptoms in schizophrenia. However, the investigators recorded data on cognition. What they observed was that for all-comers there was not an effect on cognition, which I guess was a disappointment, because let's remember that xanomeline, the muscarinic drugs in general, were actually started as therapeutic options for dementia, not so much for a psychosis. But in psychosis associated with dementia, there was an improvement, and that's how the drug pivoted from cognitive disorders into schizophrenia.

So, as I was saying, in the full sample, there was not an effect. Xanomeline did not have a procognitive effect, but when you do a post hoc analysis of individuals that started with at least one standard deviation below the norm, meaning that they have cognitive impairment associated with schizophrenia, they did see that there was a separation between the patients that were on placebo and patients that were on xanomeline-trospium, suggesting that there is indeed a procognitive effect in patients that have cognitive impairment associated with schizophrenia.

And the first question is, okay, is this specific or not? And what they saw is that it doesn't seem to be a result of just PANSS positive improvement. There's no correlation between PANSS positive improvement and precognitive effect, so it seems to be a specific and true effect, but I guess this is post hoc. There are analyses underway to confirm this.

Same thing for negative symptoms. In the registrational trials, negative symptoms separated between placebo and the active compound. If you take the patients that have the largest impairment of negative symptoms, you see a very large effect size. This is also in phase 4 trials being studied, because again, these are post hoc analyses that cannot be considered definitive.

The drug XT seemed to be very well tolerated. The side effects were related to what you would expect with procholinergic and anticholinergic drug, are either constipation, nausea, dry mouth, dyspepsia, which were present in the registrational trials in about 70%.

So to make a decision about whether this is a drug that's suitable for a patient or not, I think that we have to consider what are the metabolic adverse events that patients are experiencing on the current drug. If the patient is experiencing EPS, akathisia, tardive dyskinesia, or they're at risk of it, hyperprolactinemia, sedation, primary negative symptoms, cognitive impairment, so all of these are considerations that could make a clinician favor xanomeline-trospium as an option.

It would not be a TRS, treatment-resistant schizophrenia, prior cause being failure. There's no evidence suggesting that this drug would be helpful in individuals with treatment-resistant schizophrenia.

Patients that have medical complications that makes the gastric emptying slow, that would be sufficient to be cautious, and then the drug should be avoided, xanomeline-trospium, I mean, in patients that have absolute contraindications like retention, glaucoma, or moderate or severe hepatic or renal impairment.

The way the drug is started is by titrating as per the registrational trials, 50 mg for 2 days, then up to 100 [mg] to complete the first week, and then 125 mg going forward. The drug should be given 1 hour before or 2 hours after meals, because with a full stomach, the trospium is not absorbed, and then patients only have the procholinergic side effects, so it's recommended that patients have it with an empty stomach, and also it's important that patients consider taking ondansetron standing at least the first month to make sure that they don't experience the nausea.

It's important to be careful during the cross titration. It's recommended that patients first reach a therapeutic dose of xanomeline-trospium before decreasing the amount of the antipsychotic that's being discontinued when there's a switch. However, you have to be mindful of how much cholinergic burden you have on board. If you're coming off of a highly anticholinergic drug, you should be

monitoring for those side effects.

The speed of taper in cross titration needs to be considered as well. The data suggests from the post hoc that the phase 4 studies that the company has run that the slower titration by 25 mg per week over 4 weeks of the outgoing antipsychotic may have some advantages in terms of the mild/moderate adverse events, so discontinuing the antipsychotic over 4 weeks may be preferable than doing that over 2 weeks.

Important to note that patients are going to experience side effects. If they do, most often those happen early in the course of illness, and they usually are short lived, so for most patients the nausea and vomiting start within the first couple of weeks, and they disappear within the first couple of weeks as well. Something similar occurs for the anticholinergic side effects like dry mouth and constipation. They occur early and they are relatively short-lived.

So it's common to experience the procholinergic and anticholinergic side effects at the beginning of starting titration. It's important that we use ondansetron to mitigate nausea, that is the most common side effect. And then there are some strategies that some clinicians may use, like adding extra trospium with a prolonged titration; however, that's not endorsed by the package insert.

So, in summary, we covered that muscarinic agents target the dopaminergic system downstream more selectively than dopaminergic antipsychotics, and consequently may have more favorable side effects, along with some advantages in cognition and negative symptoms.

The use of muscarinic antipsychotics may be particularly helpful in those who struggle with negative and cognitive symptoms, and/or experience the usual side effects of dopaminergic antipsychotics, like weight gain, sedation, etc.

And finally, titration is a critical period for successful implementation of treatment. It's very important to make sure that patients do take the medication with an empty stomach, that they use ondansetron as needed to mitigate nausea, to know that they should expect it, but that's limited and benign, so they should hopefully be expecting it and tolerate it for the first few weeks. It gets better over time.

Thank you for joining me, but our time is up. This has been CE with GLC.

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