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Case Study: What Do Augmentation and Switching Strategies Look Like in Real-World Clinical Practice?

Announcer:

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Dr. Citrome:

Hello. I'm Dr. Leslie Citrome, Clinical Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York. We're going to talk about augmentation and switching strategies and what they look like in real world clinical practice. I'll base this on a case study.

Let's meet Michael. Michael's a 45-year-old man with schizophrenia. He lives in a group home and receives services from the local Assertive Community Treatment team. In the prior 2 years, he has had 3 psychiatric hospitalizations because of exacerbations of hallucinations and delusions. He is currently receiving risperidone, 5 mg at bedtime, but he complains of erectile difficulties. The staff at the group home remarked that Michael appears to be less interested in social activities at the home. What medication options can be considered?

We can actually look back in time at a clinical trial called CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness, and this tested switches amongst people, just like our case patient. CATIE examined what would happen if someone was randomized to receive either olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine, and that they could receive it for up to 18 months. About 1,500 patients participated in phase 1 of the CATIE trial. Now, patients who participated understood that they could be switched to something else if the drug that they were initially randomized to did not work, was not tolerated, or they simply wanted to switch. Then they entered phase 2, where they could enter a pathway where they could receive clozapine or olanzapine, quetiapine, or risperidone, or a pathway where they can receive ziprasidone or olanzapine, quetiapine, or risperidone. All these medications that I've mentioned so far are now available generically.

Phase 1 allowed the patient to see what would happen if things didn't work out, and went on to phase 2. And if that didn't work out in phase 2, they could receive yet another medicine in phase 3. This study, Clinical Antipsychotic Trials of Intervention Effectiveness, examined switches.

Switching can address effectiveness, a term used to describe real-world benefit and includes efficacy, tolerability, and patient preferences. The main outcome measure in CATIE was time to all-cause discontinuation, and that can include considerations of efficacy, tolerability, and patient preferences. It was observed that different outcomes were seen for the different antipsychotics tested, depending on the clinical context. Overall, olanzapine had advantages in terms of all-cause discontinuation and efficacy. Quetiapine and olanzapine had advantages in terms of all-cause discontinuation in one phase of the study where patients had failed perphenazine, a first-generation antipsychotic. Clozapine was superior to risperidone and quetiapine for patients who discontinued a second-generation antipsychotic because of poor efficacy. The bottom line, though, was that risperidone seemed to have advantages in overall tolerability

in many phases of the CATIE trial. Ziprasidone, however, had the most benign metabolic profile, and in one of the phases, was associated with a higher likelihood of weight loss for those who had gained greater than 7% of their initial body weight in phase 1.

There's additional information available from other clinical trials. A small randomized trial tested whether augmentation with olanzapine would be superior to switching to olanzapine among early non-responders to risperidone, and whether augmentation with risperidone would be superior to switching to risperidone amongst early non-responders to olanzapine. Well, it turned out that switching to olanzapine amongst early non-responders to risperidone might have a small advantage over augmentation with olanzapine. While augmentation with risperidone might have a small advantage over switching to risperidone amongst early non-responders to olanzapine.

There's a lot of information here to consider, and one of the decision points we need to make is what to do about our case patient. Do we keep risperidone? Do we augment risperidone? Do we switch to another antipsychotic? Well, before we do any switching, let's take another look at combinations. In a meta-analysis, antipsychotic augmentation was superior to monotherapy regarding total symptom reduction. However, this was only apparent in open-label and low-quality trials, and not in the double-blind and high-quality trials.

So what do we do about this information? Well, we need to look at specific outcomes here. Is it all-cause discontinuation? Is it global clinical impression? Is it positive symptoms, general symptoms, depressive symptoms? What's going on here? Because in the end, study-defined response was similar when we compare augmentation with monotherapy. There's one exception, though, negative symptoms improved more with augmentation treatment, specifically augmentation with aripiprazole. It turned out that few adverse events emerged that were different amongst the groups. D2 antagonist augmentation was associated with less insomnia, however, but more prolactin elevation, whereas aripiprazole augmentation was associated with reduced prolactin levels and body weight. So although few adverse effect differences emerged, there were some.

It seems that the data suggests that the common practice of antipsychotic augmentation in schizophrenia lacks double-blind and high-quality evidence for efficacy, except for negative symptom reduction with aripiprazole augmentation.

So bingo for Michael here. He's currently receiving risperidone 5 mg at bedtime, but complains of erectile difficulties, maybe because of elevation in prolactin. The staff at the group home remarked Michael appears to be less interested in social activities at the home, may be negative symptoms. If hyperprolactinemia is the root cause of Michael's erectile dysfunction, adjunctive aripiprazole may be helpful, a combination approach. Adjunctive aripiprazole may also help with negative symptom reduction.

However, if Michael has clinically relevant antipsychotic-associated weight gain, if that was a problem, the CATIE trial suggests that switching to ziprasidone may help. If Michael has persistent symptoms of psychosis, for example, hallucinations and delusions, the CATIE trial suggests that clozapine may help. If we're worried about treatment-resistant schizophrenia, the TRIPP guidelines recommend a prospective trial with a long-acting injectable antipsychotic.

So we do have some options here for Michael, depending on what the presenting problem is, what his preferences and values are, and the availability of these medicines on our formulary. Everything so far has been discussing generic medications.

What happens if you switch though and then switch back? Well, let's talk about a branded product that is currently very attractive in terms of its weight gain profile. Lumateperone is a mechanistically novel agent that's FDA approved for the treatment of schizophrenia. It binds to dopamine D2 receptors with lower affinity than it does to serotonin 5-HT_{2A} receptors, about a 60-fold difference. So this is quite a different molecule than what we're used to prescribing. An open-label study investigated the short-term safety and tolerability of lumateperone in outpatients with stable schizophrenia who were switched from previous antipsychotics to lumateperone 42 mg once daily for 6 weeks. Then patients were switched back to their previous approved antipsychotic. Amongst the 300 patients or so that were switched to lumateperone, there were significant decreases from prior antipsychotic baseline in total cholesterol, low density lipoprotein cholesterol, body weight, and prolactin. Most of these parameters, though, worsened within 2 weeks of resuming the other antipsychotic treatment.

So lumateperone may be an option for our case patient as well, in terms of the prolactin issues, but we need to keep the patient on lumateperone. When we switch back, we lose what was gained.

So in conclusion, there are many options that we can apply to Michael's situation, augmentation or switch. None of these are absolutely perfect. We need to actually identify what exactly Michael desires in a treatment and then apply the best solution. I hope this has been helpful. Till the next time you.

Announcer:

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