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Emerging Antipsychotic Strategies in Bipolar I Disorder and Schizophrenia: Translating Findings from Clinical Trials to Individual Patients

Announcer:
Welcome to CME on ReachMD. This activity, entitled *"Emerging Antipsychotic Strategies in Bipolar I Disorder and Schizophrenia: Translating Findings from Clinical Trials to Individual Patients,"* is provided by Prova Education and is supported by an independent educational grant from Alkermes. Before starting this activity, please be sure to review the disclosure statements as well as the Learning Objectives.

Here's Dr. Correll.

Dr. Correll:
Welcome. In this first chapter, we'll be covering the comparative efficacy data and the unmet treatment needs of bipolar I disorder and schizophrenia. I'm Dr. Christoph Correll.

Dr. Citrome:
And I'm Dr. Leslie Citrome.

Dr. Correll:
Well, let's get started. Les, can you please provide us with some background information on the treatment needs for bipolar I disorder and for schizophrenia?

Dr. Citrome:
Well, basically, we need medicines that work, that reduce symptoms. But they also have to be tolerable and safe. And moreover, the patient has to adhere to them. So, there's really three components to success, here. The medicine or intervention has to work and reduce symptoms, it has to be tolerable and safe and the patient's values and preferences have to be taken into account. So, that's the basic ingredients in figuring out something, whether or not it'll be successful or not in day-to-day clinical practice.

And we know a few things about comparative efficacy of various antipsychotics, for example. We know that they're all generally going to reduce symptoms to a similar amount. Now, some may work a tad better than others, like olanzapine, but in general, we're going to have the same broad range of reduction of symptoms, and I think this is true for both schizophrenia and bipolar mania.

However, they do differ in terms of tolerability, and we have a number of trials that have demonstrated this. For example, the CATIE trial in people with chronic schizophrenia – these were outpatients with schizophrenia – the outcomes looked fairly similar in terms of decreases in symptoms, but there were some slight changes. But the broadest differences were seen in tolerability. And we know that, for example, olanzapine is more associated with weight gain and metabolic abnormalities than some of the others. And we do know that risperidone and paliperidone, in general, are more associated with elevations in prolactin than some of the others. And we do know that quetiapine is more associated with sedation than some of the others. So we do have some differences in tolerability that vary greatly.

Basically, though, the problem is patients may get a reduction of symptoms, and they're happy at first, but then they have to live with this medicine. And after a period of time, once the acute episode has more or less resolved, they're left with lingering adverse effects that they may be quite troubled by and may not want to continue medicine and thus discontinue. This is a big problem.

Dr. Correll:
As you mentioned in the CATIE trial, there were relatively few differences, but olanzapine did come out as being the one where the patients voted with their feet; they stayed on it longer. But it had a lot of weight gain problems. And I think many of the meta-analyses, both for schizophrenia and bipolar disorder, show that, as you mentioned, that olanzapine comes up in the upper third or even the upper quintile in terms of efficacy, but side effects, particularly weight gain and metabolic problems, can be limiting. And this applies both for the acute and maintenance care in schizophrenia and the acute and maintenance care for bipolar I disorder.

The preventable risk factor for relapse can be nonadherence, which is related, often, to side effects. And the side effects most commonly observed with second-generation agents are, as you mentioned, prolactin elevation and sexual side effects, also, EPS [extrapyramidal side effects] and akathisia with some. And we have sedation, weight gain and metabolic abnormalities. And each of those can be related to poorer functionality, quality of life, as well as nonadherence.

This has been great, Les. Before we wrap up, can you please provide us with one key takeaway from this chapter?

Dr. Citrome:
Well, we talked a lot about different tolerability profiles, but keep in mind, not everyone's going to get those side effects. And we're always going to have people who don't seem to fit the mold; they don't get any side effects. And on the other hand, we get patients who get side effects that they're not supposed to get, if you read the product label.

Dr. Correll:
Thank you. In Chapter 2, we'll be discussing current and emerging data on antipsychotic-based treatments. Stay tuned.

Dr. Citrome:
Welcome. In the first chapter, we covered the unmet treatment needs of antipsychotic therapy. In Chapter 2, we'll be discussing clinical trial data of current and emerging antipsychotic therapy for bipolar I disorder and schizophrenia. I'm Dr. Leslie Citrome.

Dr. Correll:
And I'm Dr. Christoph Correll.

Dr. Citrome:
Well, let's get started. Christoph, can you please discuss the key clinical trial data on emerging approaches that may improve adherence among patients who require treatment with oral antipsychotic therapy?

Dr. Correll:
Yes. Nonadherence is a real problem, and to improve adherence, we can either give long-acting injectable antipsychotics that help us to know when a person stops and also has more sustained blood levels, but another strategy is really to improve the adherence by improved adverse effect profile. Because the majority of people are not receiving long-acting injectables, and since the reduced side effects can improve adherence, we can thereby indirectly improve quality of life, functionality, and also physical health.

So, in this context, what is the proposed value of the combination of olanzapine/samidorphan? Well, the target is to retain olanzapine's remarkable efficacy but to reduce its cardiometabolic liability. How can this be achieved? By adding samidorphan, which is a new opioid antagonist to olanzapine and making this a combination treatment. The new opioid antagonism clinically translates into a reduction of appetite and also alters the set point for satiety so that people on olanzapine gain less weight. Has that been shown to be true? Yes, it has, in a phase 2 trial that was 12 weeks in duration; a phase 3 trial that was 6 months in duration. And those were for weight gain as the target comparing olanzapine/samidorphan with olanzapine and then also an acute trial which compared in 4 weeks, olanzapine alone with olanzapine plus samidorphan and placebo. What did these trials show? In the acute efficacy trial, it was really good to show that although there's a centrally active component added to olanzapine, the new opioid antagonist, it did not detract at all from the efficacy related to schizophrenia. The efficacy was very similar to olanzapine, and both were better than placebo. And that was despite a pretty large placebo effect.

In the two weight gain-reducing trials, it was shown that the olanzapine/samidorphan combination did beat olanzapine. In the phase 2 trial, about 400 patients, it was a 37% reduced increase in weight gain. And in the 6-month trial, it was actually 50% reduced weight gain in terms of both the weight gain itself, but also in terms of people gaining at least 7% or 10%. So basically, in the large trial of 560 patients, it was 4.2% weight gain over 6 months versus 6.6%, and in terms of gaining 10% of weight, which is substantial, it was 17.8% with olanzapine/samidorphan versus 30% with olanzapine. What's interesting is that it takes about 4 to 6 weeks for this effect to kick in,

so in the first 4 to 6 weeks, there is similar weight gain as olanzapine, but after that, it's almost a flat line, which is remarkable that there's no more relevant weight gain beyond those first 6 weeks. And also, in the phase 2 trial, those patients that have gained the most weight or had gained some weight in the first week of olanzapine lead-in, they benefited the most, which is clinically relevant, meaning that those that are liable to gain weight with olanzapine could then have reduced weight gain with olanzapine/samidorphan.

In the currently available trials, there were similar other side effects as with olanzapine: dry mouth, sedation, but less weight gain and increased appetite. Remarkable and somewhat unexpected, there was yet no difference in metabolic parameters, even though waist circumference was significantly lower with olanzapine/samidorphan versus olanzapine. And that's a little hard to understand, but may have to do with the fact that it takes a little longer for that effect to show, but also it may have been more protected patients in the trials because they had no more than a BMI of 30. The mean BMI after 15 years of illness was only 25, and these patients might have been protected and survivors of the metabolic parameters that change with antipsychotic treatment.

Dr. Citrome:
Well, you know, one thing to keep in mind, though, that this combination approach does not eliminate weight gain. I mean, weight gain still occurs. So for those patients where this remains a problem, fortunately, we do have other alternatives in terms of antipsychotic choices. For example, lurasidone or cariprazine or the recently approved lumateperone have very favorable weight gain profiles. But again, if that patient is responding best with olanzapine, well, that's an issue to consider, as well. Moreover, I weigh everyone every time that I see them in my practice. And that way, I will catch those who gain weight even though they're not supposed to gain weight, because there's always going to be outliers, and that's going to be important to do. No matter how friendly a drug looks in terms of its profile in weight and metabolic parameters in a clinical trial, your individual patient may behave differently, and there's always going to be these outliers. And remember, the underlying illness is not metabolically friendly; having schizophrenia or bipolar disorder will have an impact on someone's metabolic status.

With that said, let's wrap up. Christoph, what would you say would be your one key takeaway from this chapter?

Dr. Correll:
Well, olanzapine/samidorphan combination has shown to significantly decrease weight gain that is associated with olanzapine while maintaining olanzapine's efficacy. This makes the combination of olanzapine plus samidorphan a valuable treatment option for people with schizophrenia and bipolar disorder that can benefit from olanzapine treatment.

Dr. Citrome:
Thank you. In Chapter 3, we'll be discussing how to apply this clinical data into everyday practice. Stay tuned.

Dr. Citrome:
For those just tuning in, you're listening to CME on ReachMD, I'm Dr. Leslie Citrome, and here with me today is Dr. Christoph Correll. We're discussing emerging antipsychotic strategies in bipolar I disorder and schizophrenia.

Dr. Correll:
Welcome. In Chapter 2, we identified key clinical findings on antipsychotic therapy and now, in Chapter 3, we'll be discussing how to apply those clinical findings into everyday practice. I'm Dr. Christoph Correll.

Dr. Citrome:
And I'm Dr. Leslie Citrome.

Dr. Correll:
Let's get started. Les, how can we best incorporate the combination of olanzapine and samidorphan into our clinical practice?

Dr. Citrome:
Well, Christoph, I think the first question we have to ask ourselves is, "Is this patient a candidate for olanzapine, period?" And if so, then, "Should we use this olanzapine/samidorphan combination or go at it with olanzapine itself?" And this is going to be a difficult decision when this new product becomes available commercially because there's going to be some roadblocks in terms of easily accessing it, I think. It's going to be a branded product, and we know olanzapine, currently, is just a generic agent that is relatively inexpensive. But we may want to do this. We may want to go to that if this patient has a history of weight gain with antipsychotics and has concerns about weight gain, has concerns about metabolic abnormalities, and we are worried about the safety of using olanzapine in this particular patient. They may have had some experience in the past with olanzapine and got into trouble metabolically or weight-wise. And that would be a consideration for going with olanzapine/samidorphan right away. Otherwise, some clinicians will take a wait-and-see approach and see what happens in the immediate period after starting olanzapine and see which direction they're headed.

You know, a rule of thumb I've used for years is that if someone gains 2 kilos by 2 weeks or 3 kilos by 3 weeks, then I'm worried about

long-term weight gain measured 6 months from now. And I do know if I don't change anything, after 6 months, enough weight is going to be accumulated that it's going to be almost impossible to get off. But I can do something at the beginning. So those would be my initial considerations.

Dr. Correll:
Yeah, I totally agree that prevention goes a long way and also prediction of – the present predicting the future. So those that do gain weight are good candidates for the olanzapine/samidorphan combination. So patients who are currently candidates for olanzapine who gain weight, those should be moved over, in my opinion, because if you have a safer option but you want to use that agent, then why not use olanzapine/samidorphan? Especially if you've shown that this medication in a specific patient has an adverse effect that could be mitigated. But there may be other patients where now the clinicians, the families of patients, are hesitant in trying olanzapine, even though the efficacy of the other agents is not good enough for fear of the weight gain. And here, they would have a potential option that is better in terms of weight gain while maintaining the efficacy advantages that olanzapine can bring.

Well, this has been great. Before we wrap up, Les, can you please provide us with some key takeaways from this chapter?

Dr. Citrome:
Well, I've always said, you know, being able to mitigate the weight gain that is commonly seen with olanzapine would be very, very helpful clinically. You know, "we can make olanzapine great again" would be one way to look at this. But let's not forget about diet and exercise and always talk about that when starting antipsychotics and ongoing treatment with people with schizophrenia or bipolar disorder taking antipsychotics. This is going to be really important, too. Being mindful about what one eats and how one exercises will also contribute to the overall physical well-being of your patient.

Dr. Correll:
Thank you, Les. In Chapter 4, we'll be discussing strategies to improve patient-centric issues for patients with bipolar I disorder and schizophrenia. Stay tuned.

Dr. Citrome:
Welcome. In the third chapter, we talked about how to incorporate the emerging combination agent into clinical practice. In this fourth chapter, we'll be discussing the best strategies to improve patient-centric issues for people with bipolar I disorder and schizophrenia. I'm Dr. Leslie Citrome.

Dr. Correll:
And I'm Dr. Christoph Correll.

Dr. Citrome:
Well, let's get started. Christoph, what are the most common patient-centric issues for patients with bipolar I disorder and schizophrenia? How can we improve these issues and achieve long-term management goals?

Dr. Correll:
Well, I think some of the most relevant patient-centric issues are, "How do I deal with my illness?" and "How do I deal with the treatment that you give me to improve my illness?" So if my illness doesn't get better, I will feel pretty crappy and I will not be able to function. But if you leave me with side effects that also impair my functioning and quality of life, I will doubt why I should be on this medication, and then nonadherence can happen. So I think treatment-related side effects, nonadherence, impairment of functioning, poor physical health and low quality of life are all very relevant patient-centric issues. And they have also to do with, "Will I be able to go back to work? What about social interactions? Will I have friends? Will I maybe have a relationship?"

Now, long-term management goals are challenged by the triad of adverse effects, nonadherence, and physical health problems that are associated with relapse and poor illness outcomes. So practice strategies to overcome these issues include the choice of an efficacious but also safe and tolerable medication, shared decision-making on what matters to patients, monitoring of psychiatric and physical health outcomes, as well as a focus on relapse prevention and enhanced functioning. To achieve these goals, we must also pay attention to the medication treatment that is safe and effective, but pair it with psychosocial treatment options, also healthy lifestyle treatment options, and looking at psycho-education.

Dr. Citrome:
Well, Christoph, that sounds like evidence-based medicine, doesn't it? It's the incorporation of the patient's values and preferences together with your clinical experience and recognition of what's available in terms of the relevant scientific evidence. I'd like to make a plug for motivational interviewing. It's a technique where we would listen to patients, not make too many suggestions, and meet them where they are. We need to resist the urge to dictate what we want them to do. If we get a patient to buy into the decision, they're much more likely to adhere.

This has been great. Before we wrap up, Christoph, can you provide us with one key takeaway from this chapter?

Dr. Correll:
Well, to improve patient outcomes, we must listen to what matters to our patients, employ measurement-based care, keep long-term goals in mind from the beginning, target both physical and mental health, integrate medications and psychosocial treatments and target symptoms together with well-being and functionality.

Dr. Citrome:
Well, unfortunately, that's all the time we have, today, so I want to thank our audience for listening in and thank you, Dr. Correll, for joining me and for sharing all of your valuable insights. It was great speaking with you today, Christoph.

Dr. Correll:
Thanks a lot, Les. This has been really great. I hope that the audience will be able to take valuable information from this program that can enhance their care of their patients. All the best.

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