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Optimizing Outcomes & Improving Adherence: Use of Long-Acting Injectables in Early Schizophrenia

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Optimizing Outcomes & Improving Adherence: Use of Long-Acting Injectables in Early Schizophrenia” is jointly provided by the University of Cincinnati and CORE Medical Education, LLC. and is supported by an independent educational grant from Otsuka America Pharmaceutical, Inc. and alliance partner, Lundbeck

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Dr. Russell:
Preventing a subsequent psychotic episode and resulting hospitalization in people in the early phase of schizophrenia is a key public health problem with substantial consequences to the individual. Previous research has shown that second episodes of psychosis in the same individual responds less well to the same treatment. Can long-acting injectables, which traditionally have been reserved for patients at later points of their disease, be used for earlier, even first episodes of schizophrenia to achieve optimal outcomes? Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD. I’m Dr. John Russell. Joining me to discuss how we can optimize outcomes with the use of long-acting injectables in early schizophrenia is Dr. John Kane, Professor and Chairman in the Department of Psychiatry at the Donald and Barbara Zucker School of Medicine in Hempstead, New York. Dr. Kane, welcome to the program.

Dr. Kane:
Thanks very much.

Dr. Russell:
So, it’s always great to start with a big picture view of a topic. So, what do you think are the most important factors that ensure the best care and outcomes for patients living with schizophrenia?

Dr. Kane:
Well, that’s a very important question, and there are a number of factors, and one important factor is the relationship between the patient and the health care provider and also potentially the caregiver, so, you know, what kind of therapeutic alliance that we can create with our patients and their families I think is really important. So, people living with schizophrenia need to understand the nature of the illness what to expect. We refer to this as psychoeducation, and this needs to be customized to a particular patient’s needs. They, need to understand what impact the illness will have on them. They need to understand the need for medication, the need for other kinds of therapy, and how they can reduce the risk of relapse, how they can promote a recovery, and, again, it’s important for the family to also participate in those discussions, and it’s important to keep it simple and to make sure that we focus on where the patient is at that moment. If someone is acutely ill, they’re not in a position to have an extended conversation about the subtleties of the illness, but once they’ve responded to treatment, then they’re in a better position to do that.

Dr. Russell:
So, Doctor, when you’re seeing a new patient, trying to individualize care, how do you consider the available treatment options? And

how do the long-acting injectables, or the LAIs, compare to oral medicines in preventing relapse and hospitalization?

Dr. Kane:
Well, since medication is really the mainstay of the treatment of schizophrenia, both acutely and also over the long term, it's important that a conversation regarding the indication for medication and the need for long term treatment – if that conversation takes place pretty early in the therapeutic alliance, and the concept of the long-acting formulation I think is very important to introduce early so that the patient understands that this is not something that, is only given to patients who are refractory to treatment or particularly difficult to treat. We need to make sure they understand that long-acting formulations should be a routine part of the treatment. Once we decide that someone needs medication, then the question becomes, how do we ensure that they actually get the medication? And we know that in any chronic illness, taking medicine on a daily basis is a real challenge, and that's we're fortunate in treating schizophrenia that we have a number of different long-acting formulations available. In many illnesses in general health care we don't have that option, so here we should be discussing that with the patient. We should be discussing the challenges that they have in taking medicine on a regular basis, and not in a pejorative way, we're not suggesting that you're a bad person because you're gonna have trouble taking your medicine. It's just human nature, so it's important to introduce that early. The evidence is that long-acting injectable medicines are at least as efficacious as oral medicines, but I think the overwhelming proportion of the data suggests that they are superior in reducing the risk of relapse and rehospitalization. It's very important to get that message across.

Dr. Russell:
So, Dr. Kane, when do psychiatrists start using LAIs most frequently in today's practice?

Dr. Kane:
I would say that it's often too late or in some cases never. I think many, many clinicians wait until someone has repeatedly demonstrated difficulty taking medicine on a regular basis with the consequence that they have had repeated relapses, and, in fact, some of the guidelines until recently have been very conservative in suggesting that we wait until someone demonstrates repeated nonadherence, but in my view, if a patient experiences relapses, even a single relapse, that's really deleterious to their recovery, and it can really impact their ability to return to work or to school or to be a homemaker or whatever it is that they want to do. So, you know, many clinicians wait I think far too long, and at that point if the patient has already experienced multiple relapses and multiple hospitalizations, I think we've sort of lost half the battle. In one of our meta-analyses, we looked at a large number of cohort studies, in which patients were followed both on long-acting medicine and on oral medicine, and what we saw was that amongst the patients receiving oral medicine, they were more severely ill. They had longer duration of illness, greater severity of illness. So, it underscores the fact that many clinicians wait much too long before implementing a long-acting injectable medicine, and the basic idea here is that medicine is necessary to prevent relapse, and, in fact, the number needed to treat when we talk about antipsychotic drugs versus placebo in preventing relapse is 3, which is a very, very powerful effect, and once we recognize the need for medicine, then, again, we want to make sure that the patient actually gets the benefit of the medicine that we intend. So, in my view, it's never too early to start a long-acting medicine because if we can prevent even a single relapse, we've accomplished something very important, for that patient.

Dr. Russell:
So, Doctor, based on the data you just provided, a number needed to treat a 3, what proportion of patients do you think an LAI is appropriate for?

Dr. Kane:
Well I personally think that any patient for whom antipsychotic medication is appropriate should be a candidate for long-acting formulation cause we're basically talking about a method of delivery, a formulation, that ensures the patient is getting the benefit of the medicine, and if the patient is not getting an injection, the clinical team, the family, everybody knows about that immediately, so we're eliminating covert nonadherence, which is often an enormous problem. So, rather than asking, for whom is a long-acting injectable formulation indicated, I would rather ask, why not? Why is the patient not a candidate? And I really can't think of contraindication, particularly if it's explained properly to the patient so that the patient and the family really understand the potential benefit.

Dr. Russell:
So, we want to be patient-centered in all we do. When you put patients on LAIs, how do they feel about it?

Dr. Kane:
Well, I think in general there are two sort of stages to this issue in a sense. I mean, if you ask a patient how they feel about something about which they are uninformed, it's hard for them to express an informed opinion. So, if we ask patients who have never had a discussion with their clinician about long-acting injectable medicines, they'll probably have a negative attitude. It's like, "Well, why would I do that?" or "I, don't like needles, I don't like injections." On the other hand, if we talk to patients who have actually had a shared decision-making conversation with their clinician, their acceptance of long-acting formulations can be very, very high. A lot of it

has to do with the method of presentation. This is one of those situations where presentation matters. In fact, there was a study that did a discourse analysis of 33 recorded conversations in which a psychiatrist offered a long-acting treatment to a patient with schizophrenia, and the doctors focused mostly on the modality, the injection, the shot, not so much on the benefits, and, you know, the minority of patients accepted the recommendation, but then when the investigators went back and spoke to the patient again and explained it in a different way, the overwhelming majority of the patients who had originally declined said, "Okay, that sounds reasonable." So, a lot of it really is how we go about having the conversation with the patient, and if we do that well, most patients will agree to a trial, and then the studies that have spoken to patients who have actually had experience with a long-acting medication, they've generally been very favorable about their experience.

Dr. Russell:
So, how do adverse events associated with the LAIs compare with oral therapy?

Dr. Kane:
Well, we've looked at this very carefully actually in a meta-analysis of, 16 different studies involving almost five thousand patients, and of all the adverse events that were examined in these studies, 97 percent of them, did not, manifest a difference between the oral medicines and the long-acting formulations. So, there are a couple side effects that might have been seen more or less with, with LAIs but nothing, nothing really, um, that would be concerning. In fact, we also have looked at, neuroleptic malignant syndrome, which is probably one of the most serious, potentially fatal side effects that we see with antipsychotic drugs, and one of the concerns that has been raised is if someone is on a long-acting formulation, then we can't stop the drug immediately, which is something that we usually try to do when someone develops NMS, but in looking at, over 660 cases, we did not see a significant difference in fatality rates between people who developed NMS on a long-acting injectable formulation as opposed to an oral formulation, and, in fact, we found very, very few cases of patients who had developed NMS on a second-generation long-acting injectable drug. So, I really don't think that that is an issue, either, but the bottom line is, there's no reason to think that there are any adverse effects, disadvantages with the long-acting formulation, that is I think a common myth. We also need to keep in mind that someone is probably more likely to have an adverse event if they're actually taking the medicine than if they're not taking the medicine at all. So, we need to keep that in mind as well.

Dr. Russell:
So, Dr. Kane, medication adherence is a major issue with many patients with a wide variety of chronic conditions. So, how are you overcoming this challenge in your practice?

Dr. Kane:
Well, I think the first step is really to understand the basic facts that difficulty with adhering to medication is human nature. whatever the illness, whether it's diabetes or hypertension or schizophrenia it's difficult for people to take medicine on a regular basis, and even though we as clinicians think we have an excellent relationship with our patients, they're gonna have adherence problems just like everyone else, and we need to normalize that and not stigmatize it. You're not a bad patient if you have trouble taking medicine. It's human nature, and we know that a lot of hospitalizations are due to nonadherence in medication taking. We know that a lot of patients never even fill the first prescription that they get. In fact, there was a large study a cohort study that was done in Finland where they looked at two-and-a-half thousand first-episode patients and saw that half of them were not taking their medication within 60 days of leaving the hospital, their first hospitalization for schizophrenia, and they looked at the hospitalization rates amongst people taking long-acting injectable formulations versus oral formulations and showed a significant difference, so, and again, these are first-episode patients. So, I think that's very valuable in terms of putting it in perspective both how common nonadherence is and also how we can have an impact on the first-episode patient, the patient early in the course of illness, and I like to emphasize to clinicians that if you had a strategy that saved lives, reduced costs, diminished family burden, and improved functional outcomes, on what proportion of patients would you use it? Or if a loved one or close friend developed a chronic illness where medication is effective in preventing relapse with the number needed to treat of 3, that many patients with the illness do not take oral medicine as prescribed and their treating physician is unaware ofthat the most frequent reason for relapse or hospitalization is inadequate adherence, and, in addition, evidence suggests that relapses worsen outcome in prognosis. So, again, if you had a loved one or close friend with an illness that had all those characteristics, you know, what would you do? Would you remind the person how important it is to take the medicine? Would you recommend some sort of adherence therapy or motivational interviewing? Would you send them daily text reminders to take the medicine? Or would you ask if the medicine is available in a long-acting formulation? To me, it's obvious that that would be the choice. We're fortunate in the case of schizophrenia that we actually do have medicines that are available in a long-acting formulation. So, I think rather than asking, you know, who is a candidate for a long-acting medicine, we should be asking who isn't. why wouldn't we use that formulation to make sure that someone's getting the benefits of the medication that we intend?

Dr. Russell:
So, that being said, Dr. Kane, what are the most frequently used LAIs in early stage schizophrenia? And are there any studies to

support using any particular medications early?

Dr. Kane:
Well, I think that the most commonly used medicines in early phase are risperidone, paliperidone, aripiprazole, and we actually have good studies with these medicines in long-acting formulations in first-episode and early-phase patients. So, there's one study that was done at UCLA reported in JAMA Psychiatry using risperidone oral versus long-acting injectable, and the relapse rate amongst the patients taking oral medicine was 33 percent. Amongst those taking the long-acting formulation, it was 5 percent, so very significant difference. Another study that was done in Europe involved paliperidone, which was given once monthly versus oral medicine, and these were in recently diagnosed schizophrenia patients, and there, too, we saw a significant reduction in the risk of a relapse in favor of the long-acting formulation, and we recently reported on a study that we called PRELAPSE, which was a cluster randomized trial of a long-acting aripiprazole given once a month versus usual care, and that meant the doctors could be giving anything they wanted, and we focused on patients early in the course of illness. In fact almost half the patients that had less than a year of lifetime antipsychotic exposure, there were 489 patients who participated in this study, and what we saw is that amongst the patients receiving usual care, 35 percent had at least one hospitalization, and amongst the patients receiving the aripiprazole once monthly, it was 22 percent, so very significant difference number needed to treat of 7 in terms of preventing an additional relapse. So, I think we have good data involving these medicines. These medicines are well tolerated, and I think we have a very strong case to use them in early phase schizophrenia.

Dr. Russell:
So, based on that data – so why are LAIs being used for early phrase schizophrenia more often?

Dr. Kane:
Well, we've suggested that, there are a number of reasons for this. I think one of the most important reasons is that clinicians overestimate the degree of patient adherence. They, sort of see it as a narcissistic injury if the patient is not adherent because they think, "Oh, I have a very good relationship with my patient. He or she must be taking their medicine." So, I think that overestimation is important. There's also a perception that if I suggest a long-acting injectable formulation to my patient, it means that I don't trust the person to take their medicine, and that's a real misperception of, what's going on here. It's not a question of trust. It's a question of being realistic about human nature and how difficult it is to take medicine so offering someone an LAI is not going to disrupt the therapeutic alliance. I think that's what some clinicians are concerned about. I think that there's often a lack of appreciation of the advantages, that clinicians are not necessarily familiar with all of the data, and they sometimes want to see the patient demonstrate their nonadherence before they're going to recommend a long-acting formulation. I think that's a mistake because we don't want to see somebody relapse or be rehospitalized if we can possibly avoid that and I think clinicians have not necessarily been well trained in how to have these conversations. I think it's something that you need to think about, to practice, to understand really understand the data, be able to explain the potential advantages and being able to answer questions. The patients are gonna have questions, the family's gonna have questions. You have to be comfortable answering them. So I think those are some of the reasons why LAIs are not widely used in early phase schizophrenia, and I think we need to try to change that perception that they're not necessarily appropriate for patients at that phase of the illness, and I think that's a mistake.

Dr. Russell:
So, Dr. Kane, I have a two-part question for ya. So, you mentioned a bunch of different medications. Are there practical differences between starting the different LAIs as how you get started? And is there any negative aspects to using the LAIs early?

Dr. Kane:
I don't think there are any negative aspects to using them early. I think there are considerable advantages to introducing them early in the course of illness cause I think we have a better chance of avoiding relapses, and the relapses early in the illness can be particularly devastating when young people are trying to establish their careers or their education or their social relationships, etc. relapses during that period of time can be really devastating. So, fortunately we do have a number of different medications that are available in long-acting formulations, specifically risperidone, olanzapine, paliperidone, and aripiprazole. We have risperidone available in both an intramuscular and subcutaneous formulation. The intramuscular has an interval of two weeks with a three to six week oral bridge. The subcutaneous route of administration is at four week intervals with no oral bridge. We then have olanzapine long-acting formulation with a two or four week interval and no oral bridge, then paliperidone, which is available in a four week interval with no oral bridge, and then there's another formulation of paliperidone that actually can be given every three months. We would not start that until the patient has actually experienced the once monthly paliperidone for four months, but for some patients, having an injection interval of every three months could be very advantageous, and then we have two different versions of aripiprazole. The first is aripiprazole monohydrate, and that's intramuscular with an interval of four weeks and a two week oral bridge, and then aripiprazole lauroxil, another intramuscular formulation with intervals of four, six, or eight weeks with a three week oral bridge, or there's another formulation, which allows us to give a 30 milligram oral dose just once and then a 675 milligram IM dose, so that avoids the need for the three week oral bridge. So, we

have a, I think, a good series of options, and this enables the patient and the clinician to have a discussion as to which option is most appropriate for that individual

Dr. Russell:
So, Dr. Kane, we covered a lot of ground today. How would you summarize the most important points of the discussion we just had?

Dr. Kane:
Well, I think there are multiple barriers to the use of long-acting formulations early in the course of illness. We talked about some of them. I think the clinical team is a very important issue. The team needs to understand the potential benefits to be able to explain them to the patient in a coherent way. I think the treatment team needs to be trained in communication because it doesn't always come naturally to people, particularly if someone is initially resistant, and it's interesting cause a lot of clinicians, when they say, you know, why, when they're asked, "Why don't you use long-acting formulations?," they say, "Well, my, my patients would refuse or my patients have refused," and the reality is if you go about having the conversation the right way, the patient is not likely to refuse, so, you know, those are some of the barriers. I think we need to correct misconceptions about LAIs. Some patients might have negative attitudes towards injections, but they really are not that painful, and we also need to make sure there's structural support to the use of LAIs so that the clinic, has them available, they have the supplies available, and perhaps a nurse who might be available to give the injection. If not, the clinicians, the psychiatrists themselves need to be trained to give the injections. So, I think you know, knowing these barriers and trying to overcome them is really critical in improving the outcomes of people with schizophrenia cause we've, shown that the use of LAIs early in the course of illness can, can be very advantageous in terms of reducing the risk of relapse and, and hospitalization.

Dr. Russell:
Well, Doctor, those were some great points to keep in mind as we talk about a very important disease. I'd like to thank you, Dr. John Kane, for helping us better understand the use of long-acting injectables in early schizophrenia. Dr. Kane, it was great with speaking with you today.

Dr. Kane:
Thanks very much. My pleasure.

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