Optimizing the Continuity of Care in Schizophrenia: Role of Long-Acting Injectables

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PART 1: EXPERT INTERVIEW
Optimizing the Continuity of Care in Schizophrenia:
Role of Long-Acting Injectables

Program Description
Schizophrenia is a severe and disabling psychiatric illness with a lifetime prevalence that approaches 1%. It is a chronic disease, associated with ongoing functional impairment and frequent recurrence of acute psychotic episodes. The clinical course of schizophrenia is characterized by a high risk for relapse with recurrent hospitalization, frequent comorbidity of both psychiatric and general medical conditions, and an elevated risk for suicide. Furthermore, the prognosis and outcomes in patients with schizophrenia progressively decline with each successive relapse. Poor continuity and less stringent follow-up has been repeatedly shown to increase the risk for poor adherence to therapy, more frequent readmission to inpatient facilities, and poorer overall clinical outcomes. Patient, physician and system related barriers can be significant obstacles. Identification of these barriers is an important first step in empowering both health care providers and patients. This educational program will closely examine the evidence to address and develop a strategy for clinicians during this critical period, select the most appropriate therapy, and provide answers how to utilize therapies that enhance adherence and, potentially, improve patient outcomes.

Learning Objectives
After completion of this activity, participants will be able to:

• Recognize that the continuity of care is a key quality indicator for outpatient care and is essential to prevention of relapse and re-hospitalization in schizophrenia;
• Apply the evidence surrounding the significance of negative symptoms and functionality to improve outcomes in the transitional setting;
• Integrate strategies into practice which address the significance of medication adherence in transitional care;
• Evaluate the risk/benefits of long acting injectable antipsychotics as part of a continuum of care strategy.

Target Audience
The intended audience for this initiative are physicians and other health care professionals who manage patients with schizophrenia.

Disclosure of Conflicts of Interest
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The following faculty has reported real or apparent conflicts of interest that have been resolved:

• John M. Kane, MD discloses that he is a consultant for Alkermes, Eli Lilly, Forum, Forest, Genentech, Lundbeck, Intracellular Therapies, Janssen, Johnson & Johnson, Otsuka, Reviva, Roche and Sunovion.
• John Russell, MD (host) has nothing to disclose.

The following reviewers and planners have reported real or apparent conflicts of interest that have been resolved:

• Susan Tyler, MEd, CMP, CHCP, has nothing to disclose.
• Rick Ricer, MD, has nothing to disclose.
• Deborah Cole, Program Coordinator, has nothing to disclose.
• Otto Ratz, MD, has nothing to disclose.
• Christina Culbert, MSc, has nothing to disclose.

Accreditation
This CME activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and CORE Medical Education, LLC. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

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Optimizing the Continuity of Care in Schizophrenia: Role of Long-acting Injectables Part 1

Narrator:
Welcome to CME on ReachMD. This segment, Optimizing the Continuity of Care in Schizophrenia: Role of Long-acting Injectables Part 1, is jointly provided by University of Cincinnati and Core Medical Education.

This segment will focus on the care of patients with schizophrenia and its effective management, especially as those who suffer from this condition frequently transition from inpatient management to ongoing outpatient care. This educational program will closely examine the evidence about the use of long-acting injectable antipsychotics to address and develop a strategy for clinicians during this critical period and provide answers on how to utilize these therapies that enhance adherence and potentially improve patient outcomes.

This activity is offered as a comprehensive 2-part curriculum series. Part 1 is designed to provide a didactic review of the curriculum, and part 2 provides an examination and reinforcement of learnings through patient case reviews. Learners are encouraged to complete part 1 and part 2 of the curriculum.

Your host is Dr. John Russell, and our guest today is Dr. John M. Kane, Professor and Chairman, Department of Psychiatry, at the Hofstra North Shore-LIJ School of Medicine, and the Zucker Hillside Hospital in New Hyde Park, New York.

Dr. Russell:
Schizophrenia is a severe and disabling psychiatric illness with a lifetime prevalence that approaches 1%. It is a chronic disease associated with ongoing functional impairment and frequent recurrence of acute psychotic symptoms. The clinical course of schizophrenia is characterized by high risk for relapse with recurrent hospitalization, frequent morbidity of both psychiatric and general medical conditions, and greatly elevated risk for suicide. The prognosis and outcomes in patients with schizophrenia progressively decline with each successive relapse. A critical focus area in the care of patients with schizophrenia is the effective management as those who suffer from a transition from inpatient management to outpatient care. Poor continuity has been repeatedly shown to increase the risk for poor adherence to therapy, more frequent readmission to inpatient facilities and poor clinical outcomes.

Dr. Kane, welcome to our program.

Dr. Kane:
Thanks very much.

Dr. Russell:
So what aspects of the continuity of care for patients with schizophrenia are most important to produce the best functional outcomes?
Dr. Kane:
When we talk about continuity of care, I think it’s critical that we’re able to provide ongoing treatment that’s going to help a patient maintain the gains that they have made and prevent relapse, because we’re concerned that with each relapse there can be serious consequences. Their recovery maybe slower and less complete as the illness may become more resistant to treatment, and then every time someone is in the midst of a psychotic episode, there’s increased risk of self harm and homelessness and disruption of social relationships. All of these things reinforce the fact that we need to be as proactive as possible in trying to prevent relapse.

The risk of relapse is very high—that even in first episode patients, if you follow individuals for 5 years, we see that more than 80% of the patients that had at least one relapse. The single biggest predictor of who relapses and who doesn’t is whether or not they’re taking medication.

The patients who discontinue medication are 5 times more likely to relapse than the patients who continue to take medication. Ultimately, what we’re really concerned about is trying to help patients recover, by recovery we mean getting back to work or back to school or being a homemaker or doing whatever the person wants to do in the community as well as having improvement in their symptoms, but also having a social life, having hobbies, doing the things that we all take for granted.

When we look at the data on recovery in schizophrenia, we see that only about 1 out of 7 patients are achieving the kind of recovery that we’d really like to see. Continuity of care plays a critical role in achieving those goals.

Dr. Russell:
When talking about continuity, transitions of care, how does medication adherence come into play with our patients?

Dr. Kane:
Medication is a critical ingredient in the management of people with schizophrenia, and many, many studies around the world have shown that in comparison to no treatment or placebo, that medication reduces the risk of relapse and rehospitalization to a very significant degree. It’s a very powerful effect. When we have patients transitioning from one level of care to another, particularly inpatient to outpatient, we need to make sure that the patient understands the medication, why they need to take it, what the benefits are, what the risks are, etc., and we need to try to do everything we can to monitor adherence and help the patient deal with the challenge of nonadherence. It’s important to us as clinicians also because we can make erroneous decisions. If we think the patients taking medicine and they’re not responding adequately and we start raising the dose or adding other drugs or changing the medicine or labeling the patient as treatment-resistant, we’ve missed the fact that they’re not actually taking the medicine as we expected. It’s very important that we get a handle on that.

One of the challenges is that we have a hard time identifying nonadherence, because what we usually do is we...
ask the patient to tell us whether they’re taking the medicine. That’s a very unreliable approach because the patients often don’t realize themselves how much medicine they’re missing, and physicians are often mistaken in their judgment as well. Even if we go to the patient’s home and count the number of pills in the bottle that are left, we still don’t necessarily get an accurate read on how much medicine the patient’s taking. There are a number of strategies that we try to use to help patients manage this issue. We provide them with information, with websites. We try to manage the side effects as efficiently and quickly as we can. We try to make sure that we have a very good therapeutic alliance with the patient. We try to prescribe the least complicated regimen that we can, like once a day. We want to continuously be discussing the benefits and risks and trying to get a sense of what’s happening. But in the long run, these strategies are not always effective, and I think one of the most powerful strategies that we have is also the use of long-acting injectable antipsychotics.

Dr. Russell:
Dr. Kane, how do you think long-acting injectable antipsychotics should be used as part of this continuity of care strategy?

Dr. Kane:
I think since we have the opportunity to use formulations that can assure medication delivery, that also provide us immediate awareness when the patient is non adherent—because as I emphasized earlier, we usually don’t know. If someone misses an injection, then we know immediately that they’re now not getting the full benefit of the medicine, and actually, there’s no abrupt loss of efficacy if a dose is missed because it’s going to be in their system for a couple of weeks, so it gives us some time to act, and the patient doesn’t have to remember to take pills every day. I think the long-acting injectables have a tremendous role to play. I mean, there are cons in the sense that some patients are afraid of the needle pain or they’re concerned that they might have a side effect that won’t be as readily treated if they’re on an injectable medicine. Both of those things are really minimal reasons not to use it. The pain usually subsides over time; it’s not that great, and we’re not aware of any side effects that are significantly more difficult to treat if someone is receiving injections as opposed to oral medicine. We know these medicines very well. We’ve used them orally in many patients. So I think the advantages are very, very important to consider.

Unfortunately, many patients are not given the option. They’re not really informed about the possibility of getting their medicine by injection, and sometimes if they are, it’s a very perfunctory discussion. “How would you like to get your medicine by injection?” The patient says, “Well, no, I don’t like needles. Why would I want to do that?” Then the physician doesn’t really follow up on that. Sometimes you need much more information, much more discussion, motivational interviewing or what have you. Once patients try long-acting injectables, they often prefer them to having to take oral medicine every day.
Dr. Russell:
So, Dr. Kane, why do many physicians seem hesitant to recommend long-acting injectable antipsychotics?

Dr. Kane:
Well, I think there are a number of reasons. I mean, one factor is that it may be viewed as a little bit of a hassle, that you might need either to give the injections yourself or you need an infrastructure if you’re working in a clinic. Some of the medicines might need to be refrigerated. You need to have a dialogue with the patient, which may take some time to explain the potential benefits. There’s still the sentiment in the US that somehow injections are too invasive or too controlling or we’re being paternalistic, and that’s an unfortunate misperception as to the role of these medicines. We’re not trying to control the patient. We’re trying to help the patient control the illness, and, if we don’t control the illness, we’re really doing a tremendous disservice to the patient. Physicians do have some hesitancy. They need to have experience. In my view, during residency training we should have some teaching about the use of long-acting injectables so people are comfortable with them. Now we have many options. There are a number of different drugs that are available in these formulations, and that makes the choice also easier.

Dr. Russell:
So often, I would imagine, a lot of these injectables are given in people’s primary care offices. How do you think is a good way to reach out to primary care offices who might be administering some of these drugs and partnering with their psychiatric partners with care of these patients?

Dr. Kane:
I think the reality is that a lot of these patients are not seeing primary care doctors and they’re getting their injections in a community mental health center or possibly in a psychiatrist’s office. I think there may be some situations where the primary care doctor is involved. But in my view, I do believe that a psychiatrist, a specialist, is necessary to treat many of these patients. Now, if it’s a matter of geography, and someone’s doing well, then having someone else administer the medicine—whether it’s a primary care doc or a pharmacist or what have you—that’s fine; but there should be a psychiatrist who’s overseeing the entire process. They’re the ones who need to help the patient make the decision as to whether or not to use these medicines.

Dr. Russell:
Dr. Kane, are there any guideline recommendations for the use of LAIs?

Dr. Kane:
Yes, several of the national societies and other groups have come out with guidelines, and I guess in my view the guidelines tend to be a little bit conservative in the sense that they often look for patients who have had recurrent relapses related to nonadherence. I guess my view is that once someone’s had multiple relapses, that we’ve kind of lost part of the battle. I would like to see them used somewhat earlier than as recommended by some of the guidelines.

Dr. Russell:
The guidelines do mention patient preferences as kind of one of the reasons for using them, correct?

Dr. Kane:
Yes, you’re absolutely right; but patients are not spontaneously going to come in and say, “I would prefer to get injections.” That would be unusual. I think they need to be educated about it. They need to understand what the options are, how these medicines are administered, how frequently. I don’t think we have too many patients
coming in and asking for them just spontaneously.

**Dr. Russell:**
Overall, what do you think are psychiatrists’ and patients’ attitudes regarding the use of LAIs?

**Dr. Kane:**
Well, we’ve seen from some studies that the physicians’ attitudes correlate very highly with their knowledge about the long-acting injectable antipsychotics. We need to educate doctors more about the potential advantages. The psychiatrists often overestimate how often they have actually had these conversations with patients, because what the patients tell us in surveys that have been done is that the doctor didn’t really tell them about this or they didn’t really feel they had gotten a sufficient amount of information. Once patients get that information, they’re much more likely to express their willingness to give it a try.

**Dr. Russell:**
Usually, LAIs are being used in the later stages of schizophrenia. Is there a reason for us thinking about LAI use earlier in the disease course?

**Dr. Kane:**
Yes, there are several reasons. I mean, one is that studies have shown that the percentage of time spent experiencing psychotic symptoms in the first 2 years is the strongest predictor of long-term symptoms and disability. We’ve also seen that with subsequent exacerbations, patients may experience a decrease in their treatment response. They also have a loss in vocational and psychosocial adjustment. In addition, there’s even a suggestion that there are neuropathological brain changes that might progress with subsequent clinical relapses so that the longer someone experiences psychosis, the more likely they are to see undesirable changes in the brain, and long-acting injectable medicines can help us get a handle on that. They also give us the opportunity to allow for very rapid identification of nonadherence, whereas when someone is taking oral medicine, we don’t necessarily know, and we might find out when somebody calls us from the emergency room. “Dr. Jones, your patient is in the ER.” That obviously is something we’d really like to prevent.

Now, there have been a couple of analyses from large datasets which have looked at patients treated with long-acting injectable drugs, who are within 5 years of illness onset, and they were compared to those who were on long-acting injectable drugs but after more than 5 years had passed since the onset; and what was found was that those patients who were treated earlier did better in terms of longer time to relapse, greater improvement in symptoms, higher remission rates, etc., and this was done in 2 different data sets involving 2 different long-acting injectable drugs—one was olanzapine and one was risperidone. That’s a very important message to us to consider the use of long-acting injectable drugs earlier in the course of the illness where they might have some very, very real advantages.

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**LAI Antipsychotic Use – Guidelines Recommendation**

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<th>Guidelines</th>
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<tr>
<td>American Psychiatric Association (APA)</td>
<td>Patients with recurrent relapses related to non-adherence are candidates, or patients who prefer LAI</td>
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<tr>
<td>Schizophrenia Patient Outcomes Research Team (PORT)</td>
<td>Consider LAI for patients who have a history of frequent relapse on oral medication, or history of problems with adherence, or who prefer LAI</td>
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<tr>
<td>Texas Medication Algorithm Project (TMAP)</td>
<td>Consider LAI when patients are inadequately adherent at any stage</td>
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<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>Adherence doubtful or known to be poor</td>
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Dr. Russell:
And there are studies that show relapse risk is related to adherence?

Dr. Kane:
Yes, absolutely, and we also have studies showing that the earlier introduction of long-acting injectable drugs may have a more significant impact than introducing it later.

Now, there is some confusion which we need to acknowledge in that some of the randomized controlled trials comparing long-acting injectables and oral medicine do not show the superiority of long-acting injectables; on the other hand, the mirror image studies and many of the naturalistic studies do show an advantage. This gets a little bit technical in terms of the design and methodology of clinical trials. But when you’re studying something like adherence, the varied participation in a controlled trial can have an impact on the outcome that you’re trying to study, and particularly in a controlled trial where patients are seen more frequently, they’re given reminders, they undergo frequent assessments, they have to sign a consent form. There are a lot of things that influence the ecology of care that are not necessarily reflective of real world circumstances. I still believe that we can have real advantages using long-acting injections, even though the controlled trials may not be the best way to demonstrate that.

Dr. Russell:
What LAIs are presently available in the United States, and what are the similarities and differences between them?

Dr. Kane:
We have a number of different medicines, both first-generation fluphenazine and haloperidol, and so-called second-generation drugs—risperidone, paliperidone, olanzapine, and aripiprazole are all available in long-acting injectable formulations, and the differences are basically the differences among these drugs. I mean, we know these drugs well; we’ve been using them for years; we know their potential side effects, etc., etc., there are no surprises really with patients getting long-acting injectable drugs. The other differences are in terms of what’s the interval between injections—in some cases it’s 2 weeks, in some cases it’s 4 weeks. Whether one needs to provide some overlap with oral medication that may differ from one drug to another whether it’s administered in the gluteal muscle or the deltoid. Those are some of the potential differences—time to steady state, things like that. But none of these differences are deal-breakers. I mean, they’re all things that clinicians need to understand, and they’re going to make a choice with the patient about which drug is most likely to be beneficial to them.

Dr. Russell:
Besides the benefits, certainly we were always interested in potential adverse effects. Could you elaborate on those?

Dr. Kane:
It’s important to recognize that the long-acting injectable formulations are really just different formulations of the same medications that we’re accustomed to using. We’re very familiar with the potential adverse effects of drugs like risperidone, paliperidone, olanzapine, and aripiprazole. When we do put those medications into a long-acting injectable formulation, then some patients might experience an injection-site reaction or pain on the injection, but those are relatively minor, and in fact, the pain tends to diminish over time. What we see is really this kind of same pattern of side effects that we would expect to see with the oral formulation, and we would
also assume that patients have received at least some exposure to the oral formulation before they receive the long-acting injectable. One question that often comes up regarding side effects is, “Well, what if a patient who has received a long-acting injection does develop a side effect; what can I do to manage that side effect when the medication is still in the patient’s system?” The reality is that there are no adverse effects, even serious adverse effects, like neuroleptic malignant syndrome that cannot be managed adequately, even when someone is on a long-acting injectable formulation. For example, we’ve looked very carefully at the data on neuroleptic malignant syndrome, and there is no evidence that the fatality rate is worse among people getting a long-acting injectable medicine than it is among people getting an oral medicine. Now, of course, that assumes that you’ve made the diagnosis and that you’re managing the patient appropriately. My overall conclusion to that question is that the side effects are similar to what we see with the oral medications, and these medications are well known to us; they are well tolerated, and we will see side effects that we might expect, based on our experience with the oral medicine.

One thing that we’ve also noticed is that some of the more recently developed long-acting injectable medicines are associated with less subjective pain, as rated by patients, on a visual analog scale. I think this is due to the fact that the newer formulations are not oil based. They’re less viscous and easier to inject. That partially explains the reduction in pain that we’re seeing amongst the patients receiving these formulations. As I mentioned earlier, I think pain is also likely to go down over time, as patients are more comfortable and more relaxed receiving the injections. In our experience, pain is not a major problem or obstacle to the use of these formulations.

Dr. Russell:
Could you comment on data available from head-to-head trials that have compared different long-acting injectable medicines?

Dr. Kane:
There are relatively few head-to-head comparisons of different long-acting injectable formulations, and I think when these medicines are developed they’re usually compared against a placebo, for example, in relapse-prevention trials. The data are quite consistent when you look at paliperidone, olanzapine, aripiprazole, risperidone in their long-acting injectable formulations, they’ve all shown a significant superiority over placebo in terms of relapse prevention. When we look at those trials from a sort of meta-analytic standpoint, and we look at the number needed to treat, they’re all quite similar. In my view, there are not major differences amongst these medicines in terms of their ability to prevent relapse or rehospitalization. They do differ somewhat in terms of side effects, as we would expect, from what we know about the oral formulations, and one head-to-head comparison that was published last year involved long-acting injectable paliperidone in comparison to long-acting injectable haloperidol. There was no significant difference in what was labeled as efficacy failure, which included things like psychiatric hospitalization, or need for crisis stabilization, or increased frequency of outpatient visits, etc. There was no significant difference in that regard, but there were some significant differences in terms of adverse effects. For example, patients receiving paliperidone were more likely to gain weight. Patients receiving haloperidol were more likely to experience akathisia. Patients receiving paliperidone were more likely to have prolactin elevation.

Again, those are not surprising in terms of what we know about these medicines when we give them orally, and I think the decision, as to which one of the long-acting injectable medicines should be used, is similar to the decision that we would make regarding oral medicine.

Other studies that are relevant – there are a number of different ways of looking at the impact of long-acting injectable medicines, but one strategy that’s been quite consistent in showing the potential value of long-acting injectable medicines is the so-called Mirror Image study. What that entails is taking individuals who have been treated with oral medicines, and then switching them to long-acting injectable medication, and comparing rates of relapse or rehospitalization in the interval prior to the switch, to the interval after the switch, and that’s why it’s
called a mirror image.

For example, if you look at prior to the switch, and then compare that to after the switch, you can see what impact using a long-acting injectable formulation has had on the risk of relapse or rehospitalization. It’s not the perfect design, even though each patient serves as his or her own control; it’s possible that other things are changing during the course of the trial. But I think this design can be a powerful one in supporting the potential value of long-acting injectable medicines, and we have seen that they consistently demonstrate their superiority. Now we’d obviously like to see that confirmed in other types of studies, but doing other types of studies can also be difficult and not always provide the generalized ability and kind of real-world applicability that we’d like to see. By and large, we have an overwhelming amount of data showing that these medicines are efficacious in comparison to placebo and demonstrating their potential to reduce the challenges that we have in managing patients.

Dr. Russell:
Looking towards the future, what are the most promising new LAIs in development, and what would be their advantages over those that we have presently available?

Dr. Kane:
Well, there is a once monthly injectable aripiprazole that’s under development in addition to the one that’s already on the market, and again, similar adverse effect profile to oral aripiprazole, and there’s also a 3-month injectable paliperidone that has recently been approved by the Food and Drug Administration; and that, I think, is a potential advantage for some patients to be able to only get an injection once every 3 months or 4 times a year. I think that can be very helpful for some patients. We probably want to treat them first with a once-monthly formulation and then transition them to once every 3 months. But to be able to tell a patient, “Look, you only have to come in once a month” or “once every 3 months for an injection,” I think that can make treatment a lot easier for them.

Dr. Russell:
Dr. Kane, could you summarize and go over the most important points you think we covered in our discussion today, and what would be the learning points you’d want our listeners to take away from our talk?

Dr. Kane:
Well, we need to emphasize that the prevention of relapse remains a major unmet need in the treatment of schizophrenia, that nonadherence in medication taking is a major factor in relapse, that long-acting injectable medications provide an important opportunity to help ensure that patients are actually getting the benefits of the medication that we prescribe, and there are now an array of options that are available to meet the specific needs of individual patients. We have a number of different medicines that are available in long-acting formulations, so it gives the patient and the physician a chance to consider the pros and cons of these different medicines and hopefully decide on one that’s most likely to be acceptable to that patient.

Dr. Russell:
Dr. Kane, I’d like to thank you for discussing the role of long-acting injectables in the treatment of schizophrenia today.
Dr. Kane:
My pleasure.

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PART 2: PATIENT CASE REVIEWS
Optimizing the Continuity of Care in Schizophrenia:
Role of Long-Acting Injectables

Program Description
The clinical course of schizophrenia is characterized by psychosis, with a high risk for relapse resulting in recurrent hospitalization, frequent comorbidity of both psychiatric and general medical conditions, and an elevated risk for suicide. It has been shown that the prognosis and outcomes in patients with schizophrenia progressively decline with each successive relapse. A critical focus area in the care of patients with schizophrenia is its effective management as those who suffer from the condition frequently transition from inpatient management to ongoing outpatient care. It is known that adherence to antipsychotic therapy is not optimal as many patients discontinue therapy, greatly impacting the potential for remission and prevention of symptom recurrence. Poor continuity and less stringent follow-up has been repeatedly shown to increase the risk for poor adherence to therapy, more frequent readmission to inpatient facilities, and poorer overall clinical outcomes. Available data suggests that approximately 40% of individuals with schizophrenia remain out of care, either consistently or for extended periods of time, while manifesting significant morbidity. Patient, physician and system related barriers can be significant obstacles. Identification of these barriers is an important first step in empowering both health care providers and patients. This educational program will closely examine the evidence to address and develop a strategy for clinicians during the disease continuum, select the most appropriate therapy, and provide answers how to utilize therapies that enhance adherence and, potentially, improve patient outcomes.

Learning Objectives
After completion of this activity, participants will be able to:
• In a case-based learning format, recognize that the continuity of care is a key quality indicator for outpatient care and is essential to prevention of relapse and re-hospitalization in schizophrenia;
• In a case-based learning format, apply the evidence surrounding the significance of negative symptoms and functionality to improve outcomes in the transitional setting;
• In a case-based learning format, integrate strategies into practice which address the significance of medication adherence in transitional care;
• In a case-based learning format, evaluate the risk/benefits of long acting injectable antipsychotics as part of a continuum of care strategy.

Target Audience
The intended audience for this initiative are physicians and other health care professionals who manage patients with schizophrenia.
Optimizing the Continuity of Care in Schizophrenia: Role of Long-acting Injectables Part 2

Narrator:
Welcome to CME on ReachMD. This segment, Optimizing the Continuity of Care in Schizophrenia: Role of Long-acting Injectables Part 2, is jointly provided by University of Cincinnati and Core Medical Education.

This segment will focus on the care of patients with schizophrenia and its effective management, especially as those who suffer from this condition frequently transition from inpatient management to ongoing outpatient care. This educational program will closely examine the evidence about the use of long-acting injectable antipsychotics to address and develop a strategy for clinicians during this critical period and provide answers on how to utilize these therapies that enhance adherence and potentially improve patient outcomes.

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Your host is Dr. John Russell, and our guest today is Dr. John M. Kane, Professor and Chairman, Department of Psychiatry, at the Hofstra North Shore-LIJ School of Medicine, and the Zucker Hillside Hospital in New Hyde Park, New York.

Dr. Russell:
The clinical course of schizophrenia is characterized by high risk for relapse with recurrent hospitalization, frequent comorbidity of both psychiatric and general medical conditions, and greatly elevated risk for suicide. The prognosis and outcomes in patients with schizophrenia progressively decline with each successive relapse. This creates critical needs for better continuity of care and effective management strategies for a patient transitioning from inpatient management to outpatient care. On today's program, Dr. Kane and I will review patient cases that help address these important care needs.

Dr. Kane, welcome to our program.

Dr. Kane:
Thanks very much.

Dr. Russell:
What aspects of the continuity of care are most important to produce the best possible functional outcome?

Dr. Kane:
Well, I think the continuity of care is really one of the critical elements when we’re talking about the management of any chronic disease, and in an illness like schizophrenia, we often have periods of exacerbation,
rehospitalization and then improvement, and then another exacerbation and so forth. What often happens is that—and I think part of this is our healthcare system—that we’ve tended to focus a lot more on acute inpatient care than we do on long-term disease management, and I think some of our patients with schizophrenia suffer from that. We’ve got to make sure that we’ve got good linkages between inpatient treatment and outpatient care and that we can help ensure that a patient does not fall between the cracks after they’re discharged from the hospital. Part of that is we’ve worked so hard while they’re in the hospital to control the acute signs and symptoms usually with medication, the patient sometimes is reluctant to continue the medicine; and once they leave the hospital, they’re not getting the same degree of supervision. So continuity of care is critical, but continuity of the medication administration is a very essential element there, and that’s where long-acting injectable formulations can play an enormous role. If we can introduce that, perhaps even before the patient leaves the hospital, or at least explain to the patient that that’s going to be part of our treatment plan, it doesn’t come as a surprise to them when their new physician says, “Oh, well I think we’d like to use long-acting injections.” That can really go a long way towards facilitating the continuity of care, making sure that the patient continues to get the benefits from the medication that they started to accrue while they’re in the hospital, and make sure that they don’t fall victim to their tendency to stop taking the medicine because they feel better, they feel they don’t need it anymore. You know, sustaining the gains that people have worked so hard to achieve is really, really key; but what often happens is that the patient loses sight of the fact that the gains they’ve made were due to the medicine, and as they stopped taking the medicine, they have a tremendous risk of relapsing and losing those gains.

I can give you an example of a case of a 31-year-old male who has been diagnosed with schizophrenia for the last 7 years, and over the past 3 years has had 4 hospitalizations with each relapse being precipitated by reluctance to take medication on a regular basis; but each time he leaves the hospital he feels like he’s better, he’s got his shit together as he would say, and he’s not going to get sick again even if he stops medicine. So, the clinical team, after reviewing his history and discussing his attitude towards the medicine, raised the possibility of utilizing a long-acting injectable antipsychotic. Interestingly, the patient said that this was the first time that anyone had mentioned that as a possibility. Initially, he didn’t like the idea because he didn’t like the thought of getting injections, but after some discussion and after an explanation as to what he was losing every time he relapsed and every time he got hospitalized, he finally agreed to a trial, and then he found that it was not objectionable. The pain was not that severe, and in fact, it diminished over time, and he was very comfortable. Now he’s staying on his medicine, and the hope is that he can avoid these frequent relapses and rehospitalizations.

But the reality is that a lot of physicians don’t necessarily think about this option as early as they should. They’re reluctant for a variety of reasons. Maybe it’s a hassle. Maybe they haven’t invested the time to have extended conversations with the patient and maybe the family as well about the potential benefits. We also need to do a better job of educating ourselves about what is it going to take to improve outcomes.

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**Principles of Continuity of Care**

- Patients need to sustain the gains previously made and continue to receive whatever treatments can be helpful in that regard
- Medication is a cornerstone of relapse prevention
- Many patients, despite having had the experience of relapsing after discontinuing medication, will continue to be non-adherent
- Long-acting injectable (LAI) medications provide a strategy to assure that:
  - patients will continue to get the advantages of medication
  - clinical team will be immediately aware if there is a problem when a patient misses an injection
to increase rates of recovery, and to really make sure that we don’t lose the continuity of care.

Dr. Russell:
In your experience, how important is someone’s social network to maintain good health in the patient who has schizophrenia?

Dr. Kane:
Well, it’s absolutely critical. The families, particularly during the early stages of illness, are often very, very much involved, so they need to participate; they need to have good psychoeducation to learn about the illness; they need to understand how to communicate with the patient, what kind of expectations they should have to be able to have a realistic understanding of the illness, its treatment, etc. Then when we talk about the issue of long-acting injectable antipsychotics, the family has a very important role to play in the following sense. If you have been in a situation where you have a relative who’s had a psychotic relapse or exacerbation or even first episode and that individual is lacking in insight—so they don’t see the need for treatment—and you have to do something to get them to a hospital, sometimes it involves calling the police. If you’ve been through that experience with a loved one and that patient comes out of the hospital, you’re going to be very concerned as to whether or not they’re taking their medicine because you really don’t want to have to go through that again. You don’t want them to have to go through that again. As a result, sometimes there’s this constant back and forth. “Did you take your medicine?” “No, leave me alone, I’m a big boy.” If you have the opportunity for that individual to be treated with a long-acting injectable drug, it eliminates this enormous source of tension within the family. That alone is a tremendous, is actually a tremendous reason to consider the use of long-acting injectable drugs, and it underscores how important the role of the family is as well.

Dr. Russell:
Overall, why do you think physicians are reluctant to recommend long-acting injectable antipsychotics?

Dr. Kane:
Well, many times they assume that the patient won’t agree, and they might even say something to the patient, “How would you like to get your medicine, by injection?” The patient says, “No, why would I want to do that?” And then they give up. They really need to have an ongoing conversation, psychoeducation, shared decision-making, motivational interviewing, to help the patient understand what the potential benefits are; because initially, if you say, “Would you like injections?” most people just say, “No.” I think the physician has to also feel strongly that this is a potential benefit. They need to be educated, and what we’ve seen in the number of studies is that there’s a correlation between the physician knowledge about long-acting injectable medicine and their attitudes towards recommending it to the patient. It’s a process. They need to have experience with it. They need to understand what tremendous impact multiple relapses can have on a patient’s ability to achieve recovery and realize that they can do something to intervene in a way that will help prevent relapses.

Dr. Russell:
Dr. Kane, would there be a case for using long-acting injectable antipsychotics early in the illness course even after only one episode of psychosis?

Dr. Kane:
I think that those early relapses in the patients who have only had one episode can be devastating. Often with the first episode the person’s hospitalized and most frequently they respond well to treatment, so the symptoms are under control. Then they leave the hospital, and they might have a sort of false sense of security that now they’re fine, it’s never going to happen again, they don’t want to take medicine. So they go back to school, they
go back to work or they go back to whatever they were doing and then they get sick again because they weren’t taking medicine, and the impact of that can be really devastating. If you’ve gone back to school after one psychotic episode, are you going to be able to go back to school after a second psychotic episode, or are you going to be able to get your job back, or are you going to be able to maintain your friendships? My point is that early in the course of the illness, even just a couple of relapses can be devastating, so introducing long-acting injectable medicine can be a very powerful strategy for trying to reduce the risk of relapse.

Just a case example is a patient who had a psychotic episode while a sophomore in college. He responded well to medicine, completely remitted in terms of psychotic signs and symptoms, and planning to go back to school but was concerned about maybe having a recurrence, and he was very ambivalent about taking medicine because he was concerned that he’d have to explain it to his roommates. What if they saw him taking it, or what if they saw a medication bottle in the medicine cabinet?

The idea of receiving his medicine by injection once a month was appealing because that’s something that would alleviate the need to take pills every day, and he saw that as a good option and was able to go back to school, did not have the embarrassment that he was afraid of, and he did well. That’s an example of how it can be used early in the course of the illness.

Dr. Russell:
That’s a terrific case of that continuum of care, because if he was not going to a local university, you would have to set something up with some doctors locally and set up some place locally he could get the injections; but certainly to me it really sounds like a very perfect, perfect opportunity for someone not to have something in their medicine cabinet that their roommates could be asking them about?

Dr. Kane:
Absolutely, also, every time you take a pill, if you’re taking pills every day, every time you open that pill bottle you’re sort of reminding yourself, “I have an illness; this is something I’m worried about, I’m not happy about; it’s making me insecure.” If you go once a month for an injection, you’re not having those reminders every day.

Dr. Russell:
Would there be a role for long-acting injectable medicines in patients who might be struggling with substance abuse?

Dr. Kane:
I think there is. Sometimes people say, “Well, I don’t want to use a long-acting injectable;” the patient’s smoking marijuana or what have you. I’m actually more comfortable knowing that someone has the antipsychotic medication in their system because that can help prevent an exacerbation if someone is using drugs.

An example of that is a case of a 33-year-old male who had been ill for 9 years, but he’s also being treated for substance abuse. He goes to a group every week, and fortunately there’s a nurse who can give injections, and he accepts the idea of getting, in this case, injections every other week. He agrees to a trial and he does well on it. He finds that it’s much more convenient than having to take oral medicine every day. The clinical team feels more comfortable because they know that if he does smoke a lot of marijuana or something like that, he’s going to be less likely to get into serious trouble because he’s got the antipsychotic medication in his system.

Dr. Russell:
Dr. Kane, what impact do negative symptoms have on patient functioning?
Dr. Kane:
Well, we have learned that negative symptoms and cognitive dysfunction are 2 very powerful influences on functioning. When we talk about negative symptoms, we’re talking about things like affective flattening, alogia or avolition. Obviously, if someone is not able to work or go to school because of these things, then that’s having a tremendous impact on their functioning. Negative symptoms don’t respond as well to antipsychotic medications as positive symptoms do, but I think sometimes we can get more of a response than we expect, even in the negative symptoms. If we can get the positive symptoms under control and if we can also use medicines that are less likely to produce some of the subtle Parkinsonism that we sometimes see, that might also help alleviate what appears to be negative symptoms; so we want to use a low dose; we want to use a medicine that’s not as likely to cause Parkinsonism.

Just one case example is a patient who was prescribed aripiprazole with the hope that a dopamine partial agonist would, perhaps, have more impact on negative symptoms than other more conventional dopamine receptor antagonists. When this gentleman was switched to once-monthly injections, the problems that he had been having with adherence due to sort of poor motivation and some of the things we associate with negative symptoms, those problems were alleviated because he was getting his injections once a month. His mother thought that he was somewhat brighter, seeming more alive, more spontaneous once he was getting those once-monthly injections, and he was more involved in family activities, so that was a good outcome.

Dr. Russell:
So when we talk about continuity in transitions of care, where do you think medication adherence comes into play?

Dr. Kane:
I think it’s absolutely critical. It’s one of the things that often suffers when there’s a discontinuity in care. Patients need constant supervision in terms of the signs and symptoms of the illness, medication, side effects to medication, changes in their environmental situation, exposure to stress, what have you. They need a lot of support. They also need supported employment, supported education at times. They need family therapy, family psychoeducation. There are a lot of things that come into play, but medication is an essential ingredient. It’s often what makes everything else possible, and we need to be sure that patients are actually getting the benefit of the medications that we intend. Since nonadherence is such a frequent phenomena, the possibility, the opportunity to have a long-acting injectable formulation is something that should really be considered, much more often than it is.

Dr. Russell:
Dr. Kane, would you give us a brief summary of the presently-available long-acting injectables in the United States and compare and contrast some of the practicalities of using some of these agents?

Dr. Kane:
Sure. We’re fortunate now in that we have 6 different antipsychotic medicines available in long-acting injectable formulations, specifically fluphenazine and haloperidol, which are the so-called first-generation medicines, and then risperidone, paliperidone, olanzapine and aripiprazole, which are the newer or so-called second-generation medicines. Now, we know these medicines well. We’ve used them in their oral formulations in thousands and thousands of patients, we understand their side effect profiles, and the side effect profile of the long-acting injectable formulation is similar to the side effect profile of the oral formulation, except we have a much better control over the actual administration in the sense that we know when the patient is getting their medicine. As a result, we also have a better control over the dosage, because what happens sometimes when people are taking oral medicine is that they might miss a dose here and there; they may forget; they might take too much, etc., etc.
When someone’s on a long-acting injectable medicine, you know exactly what they’re getting, and if they do miss an injection, you are aware of that immediately and you can do something about it. There’s time to act because the medicine is not out of their system as quickly as it would be if they were on oral medicine, so you have that advantage of knowing, and you also have the advantage of having a little time to do something about it, whether it’s calling the family or doing a home visit or whatever you think is necessary.

Other differences among the available long-acting injectable formulations, there’s some that can be given in the gluteal only; some can be given in the deltoid or gluteal; some need to be administered every other week; some can be administered once a month. We also will have a once-every-3-month formulation of paliperidone, so that provides another option. There’s a difference in the vehicle, so some of these are in sesame seed oil and some are in an aqueous suspension. I think that the aqueous suspension can make the injection less painful because it’s less viscous. Some can require a supplementation with oral medicine; others may not. Some will take, perhaps, a longer time to steady state.

I think the medicines are pretty similar in terms of their efficacy, but they do differ in terms of their adverse effect profile, and that’s where a conversation with the patient informing them about the characteristics of a particular medicine, what has their experience been with medicines in general or with that medicine in particular in the oral formulation, are they particularly vulnerable to certain types of side effects, less so to others, are there certain side effects that they find particularly troublesome? With a conversation with psychoeducation, with shared decision-making, we have an opportunity to give the patient a number of choices and to be able to decide with the clinical team what makes the most sense for that individual, at least as a therapeutic trial, and then go from there.

Dr. Russell:
Well, it’s talking about patient-centeredness, and probably that’s the key to what we’re doing in every aspect of
medicine right now. I think this is just another example of shared decision-making, and having the patient?

**Dr. Kane:**
Absolutely, but they need the information. They need to be educated as to what the options are and why it might be beneficial to them.

**Dr. Russell:**
So, Dr. Kane, could you summarize and go over the most important points you think we covered in our discussion today, and what would be the learning points you’d want our listeners to take away from our talk?

**Dr. Kane:**
I think it’s very important that we recognize the extent to which long-acting injectable antipsychotics really represent a major opportunity to reduce the risk of relapse and improve long-term outcomes in schizophrenia. Despite that opportunity, what we’ve seen is that many physicians do not adequately consider this possibility, and don’t necessarily present it to their patients, even after the patient has experienced multiple relapses due to nonadherence. We believe that problems with adherence are very common in any chronic illness, particularly with an illness like schizophrenia which can affect judgment, and insight, and motivation, and with which there still is a lot of associated stigma. It’s very difficult to predict which patients will experience nonadherence, and it’s also very difficult to identify nonadherence when it occurs because patients are not always forthcoming in sharing that with us, and they may not even realize themselves how much medicine they’re actually missing. In my view, having the availability of different formulations of long-acting injectable medicines, different medicines, is a major opportunity for clinicians. I think that they have really failed to take advantage of that opportunity and for a variety of reasons. Some physicians assume that their patients won’t accept injections or that they would not like the idea of having to receive injections periodically. In fact, what we hear from patients is that they often don’t feel that they’ve been adequately informed about this option. In my experience, even many patients who were initially reluctant, once they’ve had the experience of receiving the injections, they realize, “Well this is actually pretty good and it means that I don’t have to worry about taking medicine every day. I don’t have to be reminded of my illness every time I open the medication bottle.” It has a lot of advantages for them. In my view, I think instead of asking, “Why should we use long-acting injectables?” We should be asking, “Why not?” They are appropriate treatments for many, many patients.

**Dr. Russell:**
Well, Dr. Kane, I’d like to thank you for being on the program, for reviewing some cases about schizophrenia and the role of long-acting injectables.

**Dr. Kane:**
My pleasure.