[MUSIC PLAYING]

KIMBERLY CLINEBELL, MD: Thank you, everyone. And I wanted to start by thanking Dr. Chengappa, Dr. Gannon, Dr. [INAUDIBLE], everyone that helped to support and everyone that helped participate in this project as well. So as Dr. Chengappa mentioned, I'm going to be speaking about deprescribing anticholinergic medications in schizophrenia. And this is something that we don't typically think of. We typically think of prescribing medications in schizophrenia, not taking medicines away, but as you'll see today, I think that there is an important role of taking medications away, particularly when they're causing significant side effects.

See if I can make this work, OK. So neither Ana nor myself has anything to disclose. And so what we'd like you guys to gain by the end of this presentation is we'd like you to be able to discuss the pharmacology of anticholinergic medications, including both central and peripheral effects. And we'll talk about what that means here in a minute. We'd also like you to be able to discuss anticholinergic burden and how this impacts clinical outcomes and quality of life and also how reducing anticholinergic medications can improve both clinical outcomes and quality of life in folks that are on antipsychotic medications.

So just to give everyone a little bit of a background here, I think everyone in this room is aware that antipsychotic medications are the mainstay of pharmacotherapy in the treatment of schizophrenia. And how antipsychotic medications work is through blocking the D2 dopamine receptor. So antipsychotics can have varying degrees of affinity for the D2 receptors. Some have a stronger affinity and may be more likely to cause some side effects while others may not. So there are four dopamine pathways in the brain that we typically think of. And each plays a role in either the-- in either schizophrenia or side effects, side effect profiles, from blocking these with antipsychotic medication.

So the first pathway that we typically think of is the mesolimbic pathway. And this projects from the ventral tegmental area to the nucleus accumbens. And it's this pathway that is responsible for the positive symptoms of schizophrenia. So when I say positive symptoms, we think of things like auditory and visual hallucinations. So when we block this pathway with antipsychotic medications, we see improvement in positive symptoms, so improvement in auditory and visual hallucinations.

Then there's the mesocortical pathway, which also projects from the ventral tegmental area to the cortex. And it's this pathway that's responsible for more of negative and cognitive symptoms of schizophrenia. So when I say negative symptoms, I mean like flat affect, difficulty with motivation, that sort of thing, and cognitive effects of schizophrenia meaning like cognitive slowing.

The next pathway we think about is being implicated more with side effects. So the tuberoinfundibular pathway projects from the hypothalamus to the infundibular region of the hypothalamus. And when we block this pathway with antipsychotic medications, we can see side effects, so hyperprolactinemia, obviously something that we don't want.

The last pathway is the nigrostriatal pathway. And this is sort of the pathway that I'm referring to at the bottom of this slide. And this projects from the substantia nigra to the caudate and the putamen. And when we block this pathway with antipsychotic medications, we see extrapyramidal symptoms. And so what are extrapyramidal symptoms? So extrapyramidal symptoms can range from acute, meaning like right after a medication is initiated, to subacute, so a little bit further down the line, and can also be chronic as well.

So we typically think of the first two, dystonia and akathisia, as acute extrapyramidal symptoms. And so dystonia meaning a sustained muscle contraction, which can be really painful and very distressing to patients, and akathisia meaning a feeling of inner restlessness or like feeling like they need to move. Akathisia can also be a subacute or chronic extrapyramidal symptom as well. And then so sort of further down the line, either subacute or chronic, we think of akathisia, we think of tremor, we think of rigidity or muscle stiffness. And we also think of bradykinesia, which is slowed movements.

So obviously, these are things that we all-- that we don't want. And there are some risk factors for extrapyramidal symptoms that I think it's important to talk about. So first, a history of EPS-- so if someone has had EPS in the past with an antipsychotic, if we're going to initiate a new antipsychotic, for example, that's going to put them at higher risk for the development of extrapyramidal symptoms.

High potency, first generation antipsychotics-- so these are some of the medicines that I was referring to earlier. So these more-- have a greater affinity for the D2 dopamine receptors and are more likely to cause extrapyramidal symptoms. So when we think of high potency first generation antipsychotics, we typically think of haloperidol, which is Haldol, and fluphenazine, which is Prolixin.

Also, age can play a role. So younger age, young, muscular men, these are people that are at higher risk for extrapyramidal symptoms. And in particular, a lot of the times, we think of these men getting injections of haloperidol. And so they are going to be at higher risk for EPS, and in particular, some of the acute extrapyramidal symptoms like the dystonic reaction.

Initiating a new medication is also a risk factor. And sometimes because of this, especially in folks that have a history of extrapyramidal symptoms, sometimes we'll initiate a prophylactic anticholinergic medication to help minimize extrapyramidal symptoms. But certainly, initiating therapy can cause some of those acute extrapyramidal symptoms that I mentioned on the last slide.

Titrating dose is another risk factor. So the higher we go, the longer somebody is on it, the more likely they are to develop extrapyramidal symptoms. And lastly, medical comorbidities also can be risk factors. So things like Parkinson's disease, substance use, those also play a role. And many folks, I think we have to take into account, have multiple risk factors.

So how do we manage this when somebody develops extrapyramidal symptoms. So the mainstay here to manage extrapyramidal symptoms are a class of medications called anticholinergic medications. And how they work is by blocking the muscarinic anticholinergic receptors. And they do so both centrally and peripherally. And on the next slide, we'll talk a little bit more about what that actually means. These medications can either be given by intramuscular injection. And we typically use that in folks that are having acute extrapyramidal symptoms such as a dystonic reaction that I mentioned earlier. They can also be given orally.

And so the ones that are most commonly used, probably the most common and the one that everyone here is the most familiar with is Benztropine, which is Cogentin. There's also trihexyphenidyl, which has been around for a long time. That's Artane. We tend to not use that, at least in this area so much. And then also diphenhydramine, which is Benadryl. So all of these medications can be used to treat extrapyramidal symptoms, but also, as I mentioned earlier, sometimes are used prophylactically in high risk individuals to prevent extrapyramidal symptoms.

So there are five types of muscarinic anticholinergic receptors. And as I mentioned previously a couple of times, some are central and some are peripheral. So we can see both central and peripheral side effects of these medicines. So medications that we use to treat side effects of another medication also have side effects. And I think that's one of the takeaways of this talk and something important to think about because ultimately, this is what we're trying to minimize.

So the M1, M4, and M5 receptors are all central receptors, meaning they're located within the central nervous system. And so when we block these, we can cause things like cognitive slowing, which is on top of cognitive slowing that somebody may have from schizophrenia, can cause delirium, can cause agitation, all things that we don't want. Blocking the M2 receptor can cause tachycardia or increased heart rate. And then the M3 receptor, we typically think of as like slowing the GI tract down, decreasing secretions. So things like constipation, urinary retention, dry mouth, dry eyes, again, all things that can be uncomfortable and can impact quality of life.

So this is sort of the underlying thinking behind this project is that lots of people are on these medications. They may not need to be on them. They cause significant side effect burden, both day to day and can significantly impact quality of life. And so that was sort of the basis for wanting to minimize these medications.

So what the data show is that clinical guidelines typically recommend against using prophylactic and longterm anticholinergic medications. So as I mentioned previously, if someone has a bunch of risk factors for EPS and is being initiated on a high potency first generation antipsychotic, we still might want to use a short term anticholinergic medication to prevent against EPS. But really, we shouldn't be using prophylactic anticholinergic medications for every new person that we put on an antipsychotic agent.

And we really shouldn't be using them longterm, either. So in many cases, we're able to withdraw over time. Someone doesn't need to be on an anticholinergic medication one or five years down the road. But sometimes, just because either that's what the doctor is comfortable with, or that's what the person is comfortable with, or a combination of factors, they may still be on an anticholinergic medication that they really don't need years down the line. And so that's what this project was sort of trying to prevent.

And so discontinuing longterm anticholinergic agents has shown improvements in quality of life, in memory, and in anticholinergic side effects. So those are some of the domains that we looked at in our quality improvement project that Ana's going to talk about in a second.

So we used multiple scales to look at anticholinergic side effects in the quality improvement project that we did. And like I said, Ana will talk with you a little bit more in detail what that project looked like. But I wanted to give you a little bit of background on the scales before she talks about what the project looked like. So the three things I mentioned on the last slide, anticholinergic side effects, memory, and quality of life, were really the measures that we were looking at. And we used a couple of scales to do so.

So the first one that we used was the anticholinergic burden scale. And so this is a widely used, widely validated scale. Typically, we think about it being used in the elderly as the elderly population tends to be on more medications. We tend to worry more about anticholinergic effects of medications because just with age, age is a risk factor for delirium, which anticholinergic medications can play a role in. But also with the patient population in schizophrenia, many have cognitive impairments, cognitive slowing at baseline, as a part of their illness. And so we can extrapolate from the elderly population to this population.

And so what this scale really looks at is it looks at the cumulative burden of anticholinergic medications that a patient is on. So we're not just talking about psychotropic medications. We're talking about all medications. And you'll see here in a second with the next slide, there are lots of other non-psychotropic medications that have anticholinergic effects that people are commonly on. And this sort of builds and builds and builds. And people have higher anticholinergic burden which puts them at risk for all of the side effects that we've been talking about.

So this scale assigns each medication a score from zero to three. And so the medications that have a score of zero have no anticholinergic activity. The medications that have a score of one show little to no significant effect on cognition. And I'm going to go to the next slide and then try and go back. And I'm well aware that you probably can't read anything on this slide.

But the point of this slide is the bar all the way on the left hand side are all medications with an anticholinergic burden score of one. And so in this group, we have antipsychotic agents. We have medications for allergies like Zyrtec. We have blood pressure medications. We have pain medications. So the point being there's this laundry list of medicines. And the effect is all additive. And so when people come to us, and they're on multiple medical medications in addition to psychotropic medications, we often don't think of how the medical medications can be impacting the anticholinergic burden. So there's quite a long list.

The medications that are assigned a two have some evidence of clinical anticholinergic effects. So this little-- this list is the center list there. And that's a little bit shorter. But there's some anti-epileptic medications on that list. So if somebody has a seizure disorder, or if these are being used for mood stabilization, that may contribute to the overall anticholinergic burden as well.

And lastly, category three. So this is like the worst category. You want a low number here, not a high number. So these have the highest brain-- blood-brain barrier permeability and are at higher risk of causing cognitive side effects and have a higher likelihood of causing delirium as well. So on this list, the three anticholinergic medications I mentioned previously, Benztropine, trihexyphenidyl, diphenhydramine, they all fall on this list, in addition, medications like clozapine, like olanzapine, antipsychotic medications that we use pretty frequently. And then there are other medications as well.

So again, we need to really take a look at all of the medications that someone is taking. And what Ana will talk with you about is we quantified the total anticholinergic burden for each person that we looked at in the quality improvement project. In this little box right here, the take home point here is basically that each anticholinergic medication increases the risk of cognitive impairment over time. So we want to minimize as much as we can because it's an additive effect with all of the anticholinergic medications that somebody is taking. And this can impact cognition, and therefore, can impact quality of life.

So the second scale that we used was the Pittsburgh anticholinergic symptom scale Dr. Chengappa came up with this in clinical practice years ago. And so we adapted it for this project. And so this really looks at anticholinergic medication side effects. There is a measure you can see about halfway down that looks at self-report for confusion or memory problems.

But it also looks at some other anticholinergic side effects such as dry mouth, blurry vision, urinary retention, increased heart rate, constipation, some of the things that I mentioned a couple slides ago. So this sort of takes into account all of those things. And the measures at the bottom really look at quality of life. So how intense or severe are these side effects, and how does this impact day to day functioning or quality of life.

And so all of these scales that we use-- and I'm gonna talk about one more in a minute-- but each of the scales that we used because this was a quality improvement project rather than a research study, we wanted them to be short and easy to use in clinical practice so that they could be used in the office if somebody wanted to continue to do this.

The last scale that I'm going to show you. So this is the memory impairment screen. And this is an example of a word recall which we used to look at memory. And in this case with the memory impairment screen, people were asked to recall words after two to three minutes. And so this was our memory measure that we looked at in the quality improvement project. So at this point, I'm going to turn it over to Ana. She can give you guys a little bit more background as far as the projects, how we've expanded, and what results we've seen. So thank you very much.

ANA M LUPU, PHARMD: OK, thank you, Kim, for that very helpful background, absolutely essential to understand sort of how this project came to be and how important looking at a patient's entire medication regimen really is.

So I wanted to tell you a little bit about the anticholinergic reduction quality improvement initiative. I call it an initiative because it was a couple of projects, so sort of a series over the course of four years. Started back in 2014, Dr. Chengappa had mentioned a patient that he and Dr. Clinebell had been seeing. That patient was on multiple anticholinergic medications.

And they sort of thought about the different resources available in our clinic. And the-- we had a clinical pharmacist. So they made a referral to a clinical pharmacist for additional education and to really help reduce this patient's anticholinergic burden. And we thought, hey, if we can really do this for one patient, maybe there's other patients in our clinic and our pharmacy who could really benefit from this.

And so, again, the clinic that we completed this project in was the Comprehensive Recovery Services Clinic of Western Psychiatric Hospital. That's the Oxford clinic. Some of you might be familiar with it. And our patients had mostly diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder.

So this did start with a referral. And there were a few referrals to clinical pharmacy really throughout the course of these multiple projects. But to really help make this a little bit more systematic and to allow us to reach to reach more patients, we used our pharmacy resources, our pharmacy dispensing report to pull a dispensing report to see what patients were currently on Benztropine.

And we also looked for trihexyphenidyl specifically for EPS. We looked at some other anticholinergic medications like diphenhydramine and hydroxyzine. But those were typically prescribed for different indications, so maybe anxiety or sleep or allergy. So it was sort of a-- we wanted to really keep this targeted to EPS since this was something sort of more concrete that we can look at, sort of low hanging fruit.

So we did pull a report with patients on Benztropine. And we reached out to the physicians from the pharmacy end and said, some of these patients may be-- may benefit from reduction of anticholinergic burden. The physicians then looked at the side effects that the patients were experiencing and sort of determined if it was appropriate to reduce that medication and then further referred to the clinical pharmacist for assessment.

And so the first part which was completed in 2014 and 2015, the results of that were published in the Journal of Clinical Psychiatry. And we had pretty positive results in that first part. So we decided we would expand the project. So we did another initiative in 2016 and 2017.

And I just wanted to mention that for the second part, we had-- the emails to initiate this anticholinergic burden reduction had been sent just outlining some of the results that I'm about to show you to the physicians. And in some cases, just an email was enough to prompt physicians to really look at the patient's medication regimens and to work on reducing them. And in other cases, they really felt that the patient did need the extra education and the assessment by the clinical pharmacist. In those cases, the patients were referred to me.

So let me find the remote here. A little bit about what the assessment looked like once patients were referred to me. Patients-- I saw most of the patients for one initial followup visits and then for followup visits as needed. And for some patients, it only took a month to be able to really stop or reduce their medication. Other patients required up to eight months. So it was sort of variable. We didn't have very stringent timelines.

But the biggest part, and I think the most important, was a comprehensive medication review, which I think as a clinical pharmacist, as pharmacists, we're really sort of focused on the big picture. And so we were able to use the anticholinergic burden scale that Dr. Clinebell had shown us earlier to come up with a total score of anticholinergic burden that the patient had. In a lot of cases, we had patients with scores of 10 or 12 or 15 meaning that they were on a combination of maybe a few medications with a score of 3, a few medications with a score of 1, so it all really added up.

And we also used the anticholinergic side effects scale. And I want to go back to it because I think it's pretty neat to be able to-- so this was a patient-- so the patients sort of circled the numbers. And so they were able to look at this and identify some of these side effects and see them in writing. And I think that being able to see it and then to connect it to the medication that they were taking and really being able-- for me to provide education using the scale was really essential in helping patients get on board and really feel comfortable with the medication change.

Because we all know that a medication change, no matter how small, can be really nerve wracking sometimes. And we're-- both physicians and patients can be very nervous about it. So it was nice to be able to have the scale to be able to rate not only their anticholinergic burden, but also their side effects. And so when we put that together, it really provided that nice, solid sort of visual picture for the patients and also for the physicians.

And then we did those two quality of life questions. So the lower the score, the lower the impact on quality of life, the better. The higher the score, the worse. And we looked at just cognitive impairment. Again, we didn't do these very complex screens because we wanted it to be quick and easy in clinical practice.

And there was a lot of collaboration that we did with the physicians in the clinic. And I think this is really important because when a patient was willing to reduce or stop their medication, I would reach out to the physicians. And I'd sort of give them an assessment, the full assessment, after seeing the patient. And then the physician might need to say, yeah, this makes sense, or maybe we need to cut this back a little bit slower. And so then, they would send in a new prescription. The patient would pick it up. I would assist them. And our pharmacist at Forbes would help with that. And then I would see the patients again for their reassessment. So it was really a very collaborative sort of team work process that I think led to a great success.

So just to summarize the results. In part one, so the project that we did in 2014 and 2015, we had 29 patients who were identified in our report for potential reduction. And 19 of them had a medication change. And of those 45%, so 13 actually had their medication discontinued, their Benztropine discontinued. And six of them had a dose reduction.

And then in those patients that either had a discontinuation or dose reduction, we were able to see that there was a 50% improvement in reported side effects, 40% improvement in quality of life. So essentially, there was less impact of the side effects on functioning. And there was also an improvement in memory recall.

We had similar results in the second part. But we were able to recruit more patients for this quality improvement project. So 51 patients were identified for potential reduction. And really, 3/4 of them had a medication changed, again, really speaking to the success of the collaboration. And 60% of those patients had a discontinuation. And overall, there was again improvement in side effects, quality of life, and memory recall.

We also looked at the breakdown of antipsychotic prescriptions that patients were using so the antipsychotic medications. Because as Dr. Clinebell had mentioned previously, there were certain antipsychotic medications that might be more likely to cause extrapyramidal side effects. And so we wanted to see, well, are there certain factors that can make it more likely for a patient to be able to successfully discontinue the medication?

And just to break it down for you, 65% of the participants were prescribed one antipsychotic, so 33. And 35%, so a little over a third, were prescribed two antipsychotics. And then 80% of them were on at least one second generation antipsychotic. And 43% percent of them were on at least one first generation antipsychotic.

And when we looked at the treatment factors, I think this was still a relatively small study. So we were just looking for trends and for little clues as to what can really help patients have a successful discontinuation of these medications or at least a dose reduction. And when we saw patients on a first and second generation combination or on a second generation only antipsychotic, had about an 83% percent rate of discontinuation or dose decrease.

And then patients on a first generation antipsychotic only-- oh, i know I-- I don't know how to-- use this-- I can show you. Right there, that was about a 50% rate of discontinuation or dose reduction, so a little bit to be expected. We typically associate our first generation antipsychotics with a higher risk of extrapyramidal side effects. But even in these patients, half of them were able to stop or lower their medication.

We also compared oral and long-acting injectable antipsychotics. And here we saw that those on oral had a 90% discontinuation or decreased rate, whereas those patients on a long-acting had a little bit of a lower rate. It was 60%. Pretty even, 75% between males and females. And we also found that in the non-Caucasian patients, we had a higher rate of successful discontinuation or dose reduction than in Caucasians.

So to summarize, patients whose anticholinergic burden was reduced experienced improvements in side effects, memory, and quality of life. And this was possible really across the board, even in patients who were on first generation antipsychotics, even in patients who were on two antipsychotics or on a long-acting. So there aren't any clear predictors of success. I think we really need to periodically reassess our patients for the longterm need for an anticholinergic medication and really consider reducing their dose or stopping the medication if possible.

But part of this is really being able to develop a patient-centered strategy for discontinuation of these medications, meaning we really have to look at the overall burden and provide a lot of education and support for our patients. A lot of times, patients just really needed to have somebody to talk to, to have somebody to call and check in and see how they're doing with sort of the side effects. Are you having tremors? Are you experiencing stiffness? Is there something that is just different or more uncomfortable and being able to provide that support and talk them through what was going on and also collaborate with the providers made a really big difference and then really reminding them about the side effects and the impact on their quality of life.

And then consider using assessment scales, which again, we did choose these brief ones to monitor side effect burden and to monitor improvement if possible and realistic. And with that, we would like to thank everybody who helped make this project possible, Dr. Chengappa for sort of working from this from beginning all the way till now, Dr. Gannon for really helping put this into practice in the CRS clinic, Dr. [INAUDIBLE] was very helpful with statistical analysis, Dr. Ellison was the other clinical pharmacist at the time who was working with us.

And all the CRS providers, residents, and therapists, as well as the Forbes Pharmacy, pharmacists, and staff who were very supportive and who, to this day, identify patients on these medications and refer them to me. And so we really work as a team in outpatient Oxford. And I think that really led to success. So that's it. I'm happy to take questions.

[APPLAUSE]