**NAMI Ask the Expert**
**Clozapine: Understanding Benefits & Barriers**
*Featuring Robert O. Cotes, MD*

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**Dr. Teri Brister** (00:00:00):

Terrific. So on behalf of NAMI CEO, Dan Gillison, who I usually introduce at this time, but he's not able to be with us today, on his behalf and on behalf of our board, our board president, Shirley Holloway, I'd like to welcome you to this edition of NAMI As The Expert. We hold these calls monthly, and we're super excited about today's topic and about the expert that we've engaged to provide the overview of the benefits and the challenges of clozapine. I've had the privilege of serving with Dr. Cotes on the SMI advisor clinical expert team. And I assure you, he is one of us. He is focused on helping to improve the lives of everyone affected by mental illness in his practice, and in a lot of the other work that he does. With that, I would like to turn it over to Dr. Ken Duckworth, NAMI's chief medical officer, who will introduce him officially. Ken.

**Dr. Ken Duckworth** (00:00:56):

Thank you, Dr. Brister. It's great to be here. And I see we have just over 500 people to listen to Dr. Rob Cotes, who is a friend of the NAMI family. He is the resource for the SMI advisor, which is the APA's and NAMI's efforts to connect individuals with expertise on questions related to clozapine. He hails from West Virginia. Attended West Virginia medical school, did residency at Dartmouth. And now he's on the academic faculty at Emory in Atlanta, where he both runs the clozapine clinic service and works in one of the early psychosis programs. One of the things I want you to know about Rob is at the end of this talk, I'll let you know that NAMI is going to have its first book out this fall and mostly it's individuals and what they've shared. But at the back of the book, there's 35 experts and Dr. Cotes wrote the answer to, how do I think about clozapine? Is it a last line of resort? Should it be a last resort medicine? And I'm pleased to report that the publisher thought his essay was virtually perfect and required no editing. So that's the kind of expert we have for you today. Dr. Cotes, I want to thank you for joining us, for everything you do in our shared mission.

**Dr. Rob Cotes** (00:02:17):

Thanks so much, Ken. I think the real secret is I had my wife proofread it before it went out to anybody. So I think that's how it became perfect.

**Dr. Ken Duckworth** (00:02:25):

There we go.

**Dr. Rob Cotes** (00:02:28):

So I'm really, really grateful to be here. I want to thank Terry for the invitation to talk about clozapine, something I'm very passionate about. And Terry serves such an important role on our SMI advisor clinical expert team of representing individuals and families. And she really brings that family piece into the work that we do in SMI advisor, which I think is really quite essential. I have great admiration for NAMI. I feel like I've really grown as a psychiatrist thanks to my work and collaboration with NAMI. So I just really grateful for everything that NAMI has provided me in my journey as a psychiatrist.

**Dr. Rob Cotes:**

And I think that being a... I think being sort of working with individuals on clozapine, there can be a lot of ups and downs, but I'm really often given a lot of strength from the individuals and families, especially when things are kind of going tough, it's really the individuals and families that kind of get us through. So big shout out to everybody.

Okay. So a couple of key numbers. Remember you're not alone. Feel free to reach out to the NAMI hotline 1-800-950-NAMI, or you can email info@nami.org. That's a picture of me before the pandemic. And I actually had a colleague that told me I've really gone downhill since the pandemic had began when they saw a previous bio picture of me. So that's kind of a confirmation of what I knew was happening. So that was during a different time. Disclosures, over the past 36 months, I've gotten research funding from Otsuka, Roche, Alkermes and Lundbeck, all to the organization that I work for Emory university, none to my salary. Consultant to HLS Therapeutics, Saladax Biomedical and the American Psychiatric Association.

All right. So how did I get into prescribing clozapine? Well, as Ken was mentioning, I did my residency at Dartmouth Hitchcock in New Hampshire and there I had two really amazing mentors, Dr. Allen green and Dr. Doug Norsy who were very interested in clozapine. And as I was doing my residency, I was always struck that I really didn't work with a lot of individuals who were on clozapine. So it wasn't until my third year of residency, psychiatry training is four years, where I finally identified someone that I thought might benefit from clozapine. And I was working at a wonderful community mental health center. I was part of an act team at that time. And we identified this person. I proposed clozapine and there was a lot of pushback.

I mean, there was concerns that maybe it wasn't the right choice. It really took a lot of time to convince the team that maybe this person could benefit from a trial of clozapine. And I think that kind of experience is something that other people might have too when it comes to clozapine. And I became really, really interested in clozapine. The person that we started on clozapine did extremely well. And it was always really surprising to me why clozapine was so underutilized.

So after my residency, I moved to Atlanta. I began working at Grady Hospital, which is in downtown Atlanta. We work with a large population who has no insurance or not enough insurance. And I was struck there that really no one was taking clozapine at the time. This was back in 2011. And one of my main goals and missions was to expand the safe and effective use of clozapine. So I do clinical work in a clinic called PSTAR, which focuses on clozapine. We are working with probably about 110 individuals who take the medication.

And over the years, I've given a number of talks on clozapine, and I've heard a number of talks on clozapine. And what I think happens is people get way too focused on the side effects and way too focused on what could go wrong rather than hearing about the potential benefits, the potential game changing benefits, life changing and life saving benefits of this medication. So I really want to try and hold both of those things in a balance today, the benefits, the barriers, kind of what we can do to overcome them. And as you're listening to this talk today, it's possible that you might recognize a loved one who could benefit from a trial of clozapine, and you are the most powerful person that can possibly advocate for them in order to get them onto clozapine. Not everybody's a clozapine candidate, but for who is, it can be a life changing medication.

So I want to start with the benefits. I want to highlight a number of individuals that I've worked with in a bit of a de-identified way. So some of the details are changed in these little case presentations, but this just sort of, kind of, I hope illustrates a little bit about the kind of benefit that people can experience when they get an opportunity to be on clozapine.

**Dr. Rob Cotes:**

So I was working with a 24 year old young man. He had been experiencing psychosis for three years. He struggled a lot. He had been in the hospital many times. He tried four different antipsychotic medications.

He tried some combinations of antipsychotic medications. He's an African American man. And actually his absolute neutrophil count was very low. And I think when people saw that they were concerned about starting clozapine and he was ultimately diagnosed with benign ethic neutropenia, which is another way of saying that his neutrophil count, that's the cells that fight off infection into body were basically normal and that he was able to go on clozapine. And when he did, he did extremely well. And he's right now having a lot of improvements in symptoms and in functioning and working towards getting back to school.

Another example of someone who I've had the privilege of working with, a 32 year old man with a history of multiple diagnoses, all sorts of things, schizophrenia, schizoaffective disorder, bipolar disorder. He was in the hospital many times. He also tried residential substance use treatment programs. Things got pretty rough and he had thoughts about ending his life. He'd been on multiple medications, olanzapine, aripiprazole, haloperidol, various mood stabilizers. He was started clozapine and then the inpatient stays ended. He had a significant reduction in symptoms and he's currently on well on monthly monitoring. And also a significant reduction in substance use, which is one of clozapine's other benefits, which we'll talk about a little bit.

Another example of a person that I was able to work with as a 26 year old female who struggled with unrelenting command auditory hallucinations. This person had tried olanzapine and because the medications didn't work and they caused side effects, she had long periods off of medication. She was actually in the state hospital system for a while after experiencing some significant symptoms of psychosis. There with her family's urging, she was started on clozapine and her life has completely changed. She's doing well, she's on monthly monitoring. That means that she's been on clozapine for greater than a year. She's currently working and she is in school.

But really, I think it's a lot more powerful to hear it from other people who have actually taken clozapine and to hear about their journey. And this young man Thomas here on the left is really has a remarkable story. And if you go to amiadvisor.org/individuals-families, you can hear a little bit about Thomas's journey on clozapine. I had an opportunity to interview Thomas and his family and really clozapine was a game changer for him. And he really describes the benefits that he was able to gain from clozapine in a very, I think in a very articulate way and it's a great video to check out if people are considering clozapine.

So I'm going to talk a little bit about what individuals who take clozapine actually think, because I think that there's a real gap in the literature about this. A lot of what we know about clozapine is about what do the prescribers think about it? What are the barriers, and all that's important. But I wanted to start out with this survey that we did that was recently published where we actually talked to a bunch of people on clozapine. So we surveyed 211 people on antipsychotic medications, and 86 of them were on clozapine. This was a survey that was done at Grady.

And on average, people had taken four antipsychotic medications before being on clozapine. So multiple trials, there was a lot of suffering and 72% of individuals reported that they were more satisfied with clozapine than the other antipsychotic medication that they were taking. And they also said importantly, that the blood work was less burdensome than they had expected it to be.

**Dr. Rob Cotes:**

**Dr. Rob Cotes:**

And as we'll talk about the blood work for clozapine monitoring is one of the main barriers from both a individual perspective and from the I think system and administration perspective. So one of the things I'd like to do now is outline a little bit about when clozapine may be considered as an option.

The APA practice guidelines for the treatment of individuals with schizophrenia were published in, they were published last year and they were updated. And basically, the most common reason people are prescribed clozapine is that they have minimal or no response to two trials of antipsychotic medications, not four, not eight, not 10, but two. After two trials of antipsychotic medications, it's very unlikely for other medications to work if they haven't been successful. So what happens after people don't respond to two antipsychotic medications is a condition which is poorly named called treatment resistance schizophrenia, which I think highlights a lot of what is wrong.

Treatment resistance schizophrenia is a very pessimistic nomenclature and it doesn't account for the fact that if you have somebody who has this condition, they may be prescribed clozapine and they can do quite well. So there's a, I call a lot of issues with this name, treatment resistance schizophrenia, but this is what's in the FDA package insert as one of the two FDA approved indications for clozapine use is treatment resistance schizophrenia.

So individuals with treatment resistance schizophrenia, they contribute to a lot of healthcare expenditures due to hospitalization, medications. Sometimes people have interactions with the justice system. But I think what's important to know is that in a recent study that looked at a big group of individuals with early psychosis, it turned out that 23% of them developed what's called treatment resistance schizophrenia. They did not respond to two antipsychotic medications, and they were clozapine candidates.

We also know that individuals with TRS have a high rate of suicidal ideation, smoking and substance use. So there's also multiple medical issues that can happen for people who have this condition. I vote we change the name and maybe I can get some help from folks in NAMI that we can work on making this a little bit more of a positive or at least try and change the paradigm a little bit. The name of our clinic is called PSTAR stands for persistent symptoms, treatment assessment and recovery. And I'm not saying that persistent symptoms is the best name for it either, but I think it is a little bit better than treatment resistance schizophrenia.

So just to break this down a little bit more, because if you identify someone who you think might benefit from clozapine, it's possible that the prescriber might say, "Okay, well, does this person really meet that criteria or not?" So I'm got to put these up here so you can take a look and you can see. So these are the consensus guidelines for what treatment resistance schizophrenia is. And essentially, it is a combination of current symptoms that are moderate in severity with some sort of functional impairment, two or more antipsychotic medication trials, as we discussed. And there's an antipsychotic dose that's a reasonable dose and it's taken for at least six months. And people are actually taking the medication too somewhat consistently 80% of the time.

Now for people who meet these criteria, clozapine by far is the most effective medication for them. And just to give you a little bit of perspective on that, for people with TRS, the response rate is between 40 to 60% for clozapine. For high dose of olanzapine it's zero to 7%, and then it's less than 5% for other antipsychotics. So you can see that after someone doesn't respond to two or three antipsychotics, the rate that they'll to a different non-open antipsychotic is actually very, very low. And the sooner we are able to advocate for individuals to try clozapine after less antipsychotic trials, the better and the better people might end up doing.

**Dr. Rob Cotes:**

We know based on data from all sorts of studies that clozapine has superior efficacy for treatment resistance schizophrenia for the positive symptoms. That means the delusions, hallucinations in the short term and in the long term. So in the clinic that I'm part of, the PSTAR clinic, I think since 2016, we've had about 500 referrals and 95, 90% of them are for this. People have tried other medications, but they just haven't worked for people. But there's another really, really important indication for why people might benefit from clozapine. And that is if people have a risk of suicide attempts or if suicide remains or the risk for suicide remains substantial, despite other treatments.

So clozapine is one of the few medications that we know of that can actually reduce suicide risk. And in my experience, clinicians are a lot less familiar with this one. And we get many, many fewer referrals for people who have struggled with thoughts of suicide or who have made a suicide attempt. And this specifically is for individuals with schizophrenia or schizoaffective disorder. Just to break this down a little bit more, the risk of suicide for individuals experiencing schizophrenia is high almost 5%. And it varies on different estimates, but maybe 40 to 50% of people with schizophrenia might make a suicide attempt at some point during their life. And we have clozapine, which is the only medication that actually reduces suicidal behavior and suicide attempts.

And quick shot out to Dr. Duckworth, but he was actually one of the people that was part of the investigator group of the intercept study, which helped to show this. And this was a study that compared clozapine to olanzapine and showed clozapine's superior efficacy in reducing suicidal behavior. We also know that in more naturalistic studies and in registry based studies, it turns out that clozapine is the only medication, the only antipsychotic medication that causes a decreased risk of suicide. And we also know that although clozapine has a number of side effects, clozapine also helps to reduce mortality among individuals experiencing schizophrenia.

There is another third component that the APA guidelines recommend, and that's for people with schizophrenia be treated with clozapine if the risk for aggressive behavior remain substantial despite other treatments. And I worked on an inpatient unit for about eight years earlier in my career. And sometimes people could be identified as potentially benefiting from clozapine if that was something that they... If aggressive behavior was something they experienced, either at home or maybe on the inpatient unit. There's been some really com telling studies that have shown clozapine's superior efficacy in comparison to olanzapine and haloperidol.

But that's not all. There's other ways that clozapine can help people. And I just put this list up here so you can see these are all off-label indications, but there has been some literature to show that clozapine can make a difference in these situations. One of my mentors at Dartmouth, Allen Green did a study looking at treatment resistant mania in clozapine and these are people who've had bipolar disorder, they had mania, they had persistent symptoms of mania and psychosis and clozapine was shown to be effective in those settings.

Sensitivity to extrapyramidal side effects when treated with antipsychotic medications. So some people, if they take even a lower dose of medications like Risperidone might develop things like Parkinsonism, that means like a rigidity or so some people are very exquisitely sensitive to these types of side effects from antipsychotic medications. And in those situations, clozapine may be a consideration, because it's really not associated with extrapyramidal side effects.

Earlier in my career, I used to get a lot of referrals for people who had tardive dyskinesia and continued symptoms of psychosis and we would start clozapine with them. Clozapine's not really associated with tardive dyskinesia. There's been some rare case reports that have shown an association, but really it's very, very rare. Tardive dyskinesia is in voluntary movement of the mouth or of the face.

**Dr. Rob Cotes:**

The longer people are on antipsychotic medications, the greater the risk. Clozapine is really not associated with it very much. Now there's better treatments for tardive dyskinesia. But for some individuals who have this combination, clozapine can be quite helpful. Parkinson's disease, psychosis, psychogenic polydipsia is where people drink water and they're really not able to stop drinking water and it can cause low sodium levels in their body. There is also a literature for people with severe self injury in the context of borderline personality disorder.

Also individuals with early onset psychosis or childhood schizophrenia may particularly benefit from clozapine. Psychosis and catatonia, clozapine may be one of the safer antipsychotics to use if people experience catatonia. And then also there's a relationship that clozapine may help to reduce substance use, perhaps alcohol or cannabis use in comparison to other antipsychotic medications. So there's a lot of ways that people can potentially benefit from clozapine. Clozapine, which, and we'll talk about this in a little bit, but there's a big ask I think when people think about clozapine and that's for this first six months that they take clozapine, they get blood work once a week. And that can be kind of a deal breaker for some people. But I think if people can consider making the investment in the once per week blood work, the benefits may really outweigh that for some individuals.

I want to talk a little bit now about clozapine's underutilization. So if you look at the rates of clozapine prescription for people with schizophrenia in various countries around the world, this is some data that [inaudible 00:24:41] put together. In Australia, we have 35%, China 30%, England 23%, the United States is 4%. And this is still really pretty consistent. So really only about 4% of people who experience schizophrenia are prescribed clozapine in the United States. And as I was telling you earlier, between 20 to 30% of people may actually benefit from that medication. And that's just from the failure of two antipsychotic medications having nothing to do with the whole suicide part. So there's a pretty significant gap there.

This is some additional work that's been done by Scott Stroop and Mark Olson, who found that about 5% of people with schizophrenia prescribed clozapine in the US. And these are individuals who have Medicaid as their insurance provider. And as you can see, this is another thing showing the same finding, but clozapine is underutilized in the US compared to other countries. And it doesn't really have to do with the monitoring requirements being different. Some people might say, "Well, maybe in Australia, they don't have routine hematologic monitoring. People don't have to do the blood work."

Well, they most certainly do have to do the blood work. And in some ways actually the monitoring frequency is more stringent than it is in the United States. So it's not just the blood work. There's other factors that are related to it. And you can see here, the blue arrows represent where the United States is and this blue arrow on the top is the public mental health system. And this blue arrow on the bottom is the private mental health system. And it's even more underutilized among individuals who have private insurance.

There's a lot of geographic variation in terms of where clozapine is utilized. So this is sort of a little bit of a state by state report card around where clozapine is used and where clozapine is used less frequently. And I live down here in Georgia and you can see in the south, there seems to be a trend towards even less utilization of clozapine. But really, it's not just a problem with the Southeastern United States. It's a problem all over the United States. The other thing that we know is when people don't use clozapine, they tend to combine antipsychotic medications together. So that means somebody will be on two antipsychotic medications together. And this is a practice that we call antipsychotic polypharmacy, and we published a paper and we looked at the different states and their rates of anti polypharmacy across the US.

**Dr. Rob Cotes:**

And interestingly, when people are on two or more antipsychotics, the data is really not clear whether two antipsychotics makes more of a benefit than just one antipsychotic. But we found that 32% of people with schizophrenia were prescribed two or more antipsychotics. And then if you go back, four to 5% of people were prescribed clozapine. So really doesn't seem to make much sense.

How can we overcome some of these barriers and what are the barriers in terms of getting more clozapine prescribing out there? Okay. So you can probably divide it into three buckets. These are the client-related barriers. These are the prescriber-related barriers. And then these are the administrative/logistical barriers. And for individuals, there's a number of concerns that people have about clozapine. I mean, people might hear about the weekly monitoring or they might hear about the side effects of the medicine and be like, "You know what, that's just not going to be for me."

I think that sometimes people don't hear enough about the potential benefits, but there's a number of barriers. And one of the things that we try and do a lot of is talk with people, give people access to other people who have tried clozapine and who've been successful with it. We try to get families very involved as well. We do a lot of education, a lot of shared decision making, ProCon matrix type work. But maybe we can just talk a little bit about the side effects of the medication and put that into somewhat of a context. So the side effect that most people talk about with clozapine is called neutropenia and that's when the blood cells that fight off infection become too low in the body. And when people get the blood cells that fight off infection, when that count is too low, they can be susceptible to getting infections. And when people can get infections, they can get in their blood and they can get severely ill and they can potentially die from that.

This is the reason why we get the blood work. So when we're getting the blood work, we're looking for the absolute neutrophil count. It needs to be done weekly for the first six months that people take clozapine. Then after people have been on it for six months, then it goes to every other week. Then after they've been on it for 12 months, then it goes to monthly. Now there is some question whether monthly monitoring is necessary.

Typically after a year, the risk of neutropenia from clozapine drops down to what the risk of neutropenia is for other antipsychotic medications. We know that for people who are on clozapine, neutropenia tends to happen earlier. So the peak incidence is one month after clozapine is started. And you can see here the numbers. 4% of people prescribed clozapine develop neutropenia and less than one develop severe neutropenia. And then one in 7,700 people exposed to clozapine will die from severe neutropenia. This is something that happens early again. And these risks can be mitigated when you monitor the blood... When you monitor the absolute neutrophil count closely.

Now back to the first case we were talking about. This is the individual who had what's called benign ethnic neutropenia. And for years, I think that some populations did not get a fair trial of clozapine because it was thought that their neutrophil count was too low. But what was happening was their neutrophil count was actually normal. Their neutrophil count just wasn't like the neutrophil count that was standard measured, that was kind of measured in regular, in lab tests that didn't include diverse populations.

So benign ethnic neutropenia is something that we see a good bit in the population that I work with at Grady. Neutropenia, these are in who have a neutrophil count that's usually around 1500, but it actually might not be at increased risk to develop any sort of severe neutropenia or problems from clozapine. And we know that benign ethnic neutropenia occurs more commonly in individuals of African or Middle Eastern ancestry, as well as Ethiopian and Yemenite Jewish descendant patients. And this happens in about four and a half percent of people compared to less than 1% in Caucasian people.

**Dr. Rob Cotes:**

Okay. So there are other side effects as well. Seizure, there's a risk of seizures. And then also there's a risk of myocarditis, which is an inflammation of the heart muscle that again, occurs off often early in a clozapine titration. So most of the time, myocarditis happens in week two to week three and there some special lab tests that prescribers do to help monitor for that. There are a number of other side effects that clozapine can cause, and these things happen much more commonly. And I know that there's a number of questions about this already in the chat, some of the side effects that clozapine can cause.

So clozapine is usually taken at bedtime because it makes people very... Can make people tired and sedation is a common side effects. And that's definitely a big issue that we help people manage, especially people are doing well. People are trying to work. People are getting up to go to work taking clozapine, how can we help them feel ready to go in the morning? Increased heart rate is common. Constipation is one of the really biggest issues with clozapine. I think we are very, very careful to ask people about their bowel habits and make sure they don't get constipated. There are severe medical consequences to untreated constipation, including developing what's called an ileus. And sometimes people can get very ill if constipation is not treated. And then you can see, see a number of other side effects here.

So we asked people in Atlanta kind of what were the side effects that they were experiencing. And they actually told us about over 70% of people told us that drooling was quite problematic. And this can really have a negative impact and is associated with a lot of stigma. And this is something that we often try to treat with a medication that's given under the tongue called atropine drops. And sometimes that helps with the drooling, but you can see also sedation and weight gain. Weight gain is something that also comes up a lot when it comes to clozapine. Of the antipsychotic medications, the two worst offenders of weight gain are clozapine and olanzapine. So anybody who's on clozapine, we talk with them, we spend time with visits, over half of the visits talking about diet exercise. Are there things that we do to help people feel more active?

Some medications might also help with this, including Metformin and GLP-1 agonists. So there's a number of options, but oftentimes weight gain is one of the main things that we're managing. Now that's a little bit of an overview about the side effects and we can get back to some of those. I want to talk some about the prescriber related barriers, because I think that that really contributes to why clozapine is underutilized in the United States. And it comes down to two simple things, lack of comfort, lack of knowledge I think.

People just aren't familiar with you using clozapine and I'm not here to shake a stick at anybody. And because if somebody were to say, "Rob, what do you think about prescribing ketamine to somebody?" I would be like, "I don't really know a lot about ketamine." I would probably want to refer somebody to a specialist who really focuses clozapine or sorry, focuses on ketamine. But for people who don't see a lot of individuals who are experiencing schizophrenia, they might not feel very comfortable prescribing clozapine.

So that's sort of part of the issue, but also in this sort of medical climate that we're in, a lot of times, people just don't have enough time to really talk about it, to talk about the potential benefits, to talk about the potential risks, to document everything in the informed consent process, to really give people an understanding of why this medicine might be helpful. It's very difficult to do that in a 15 minute visit or in an eight minute visit. So I'm pretty grateful that we have often sufficient time to actually have these conversations in the clinic that specializes on clozapine. But in a lot of situations, it's just not feasible. And then finally, a lack of infrastructure to help people with the blood work.

**Dr. Rob Cotes:**

To talk a little bit more about the lack of comfort and knowledge, we did a survey at a medical meeting, at a state medical meeting talking to psychiatrists about clozapine and a third of them didn't feel comfortable prescribing clozapine, and that's fine. I think that the key though is helping prescribers identify who might benefit from close Aine. And if that prescriber doesn't feel comfortable with it, they can refer to somebody else. This was a little bit concerning, but over half would prefer to combine two antipsychotic medications instead of use clozapine, which is not a practice that's supported by the literature. And then I think that there's some fear that can be associated with clozapine and over half overestimated the risk of severe neutropenia, which we talked about was 0.8 to 0.9%.

So what are we doing about this? This is where SMI Advisor comes in. We're really trying to create a community of prescribers who are going to feel more comfortable with clozapine, who might want to expand their clozapine practice. And if a person can begin to prescribe clozapine, if people can develop some expertise, increase the number of individuals they're working with, I think you can make a really big difference. So we have a lot of different ways for prescribers to learn about clozapine. We have a one to one consultation service, people ask all sorts of questions about clozapine and its side effects. What are the best tips in terms of managing side effects? Might clozapine be a good choice? We have all sorts of webinars. So if you're talking to a prescriber who's not feeling really comfortable with clozapine, you can direct them to SMI advisor in the clozapine Center Of Excellence to get more information.

So I suspect that many people who are watching this webinar may either be on clozapine or may have a loved one who is on clozapine or alternatively may be considering clozapine as a possibility. And I really think that the way that clozapine is introduced is a really important conversation. And I work with trainees in my setting. So psychiatry residents, other trainees and I've seen this done well, and I've seen it not done well. And I acknowledge, there's been times where I haven't done this well at all. But in seeing this sort of a number of times, I think that there are some key sort of components into how this discussion can happen in a better way.

And I think that framing it in the context of recovery is really, really important. We all know that medication is not everything, but medication can be an incredibly powerful recovery tool for some people and clozapine can be a really, really powerful tool in that. So I often frame really any kind of medication within a recovery context, and it's less about the amelioration of symptoms, but more about helping people get on with their lives, helping people do the things that they want to do. And for some people, clozapine can really enable them to do that.

Then there's a number of other parts of this. And I think part of it is talking about the weekly blood draws, how can you manage that? Is transportation going to be a barrier? Can point of care absolute neutrophil count tests be used, like with a finger stick? Are people afraid of blood work, people afraid of needles? So there's a number of potential barriers. And then again, utilizing the family and other supports, producing a ProCon decision matrix. There are a number of administrative barriers as well with clozapine. This is the third bucket systemwide issues. And one of the systemwide issues happens with the clozapine REMS system, which we'll talk more about in a minute. It often requires a lot of coordination with pharmacies. So the individuals have to get blood work. The prescriber has to then authorize the medication.

Then the pharmacist, so there's this sort of three kind of groups that are all really, really important in terms of getting people their clozapine, especially on a weekly basis at first. And if people don't get their clozapine, if they have a gap in their clozapine treatment, even just a couple of days, it can result in pretty bad stuff happening. People can experience flare ups in their symptoms.

**Dr. Rob Cotes:**

People can feel kind of... People can feel pretty crappy if they don't take the medication, if there's sort of a delay in getting them the medication. So there's a lot of systematic barriers.

One of the systematic barriers that there's been a lot more attention to is our healthcare disparities. And we have been increasingly learning in part from this recent systematic review is that all studies reported clozapine underutilization in ethic and racial minority patients when compared to white counterparts. So there are these disparities in care that have happened. And part of it might be related to the benign ethnic neutropenia component that we've been talking about. But I do think that there are other potential factors as well.

And one of the potential strategies to overcome this barrier is by using the AACP. It's American Association for Community Psychiatry smart tool, which is a wonderful new publication that came out last year where organizations can actually look at key clinical outcomes and try to figure out how are they doing it and can they do better in certain areas around healthcare disparities. So this is one of the things that we're looking into in our organization. Have we identified disparities in our clozapine prescribing and are we making progress with that?

Okay. We want to talk a little bit about clozapine REMS. So first of all, we probably need to talk about what a REMS is in the first place. And REM stands for risk evaluation and mitigation strategy. This is handed down from the FDA around certain medications with serious safety concerns to ensure that the benefits of the medication outweigh the risks. And there are 63 medications that currently have a REM system. Many of them are psychotropic medications, including Suboxone, Zyprexa Relprevvs, Spravato and not a psychotropic medication per se, but isotretinoin or Acutane.

Now the clozapine REM system has been designed to help reduce the risk for severe neutropenia for individuals who take clozapine. So every time I get blood work back from a person who takes clozapine, I go onto a website, clozapine REMS. I insert that number into the system for that particular person, then the pharmacist can at that system, they can look at the absolute neutrophil count value, and then they can decide to authorize the medication so long as everything looks okay. Well, in November, there were some changes to the clozapine REM system. And we went into what's called new clozapine REMS.

For those people who know someone on clozapine, that initial week was really rough. And there was a lot of issues and only after... So the new system went into effect on Monday, and then the FDA said, "Hold up. We got to do something." And on Friday, certain provisions of the REM system were suspended and certain provisions of the REM system are still suspended. So at this time, the pharmacist doesn't actually need to get what's called a REMS authorization dispense form. It's a little bit of a... It's an easier process that they're more easily able to over ride and prevent people from missing doses of clozapine. But you can see how all of this contributes to the underutilization of clozapine. I mean, some prescribers, they think about the clozapine REM system, maybe never even have used it and said, "This is just too complicated. This is going to take too much time." That should not be an answer that anyone is okay with. Okay.

I want to talk a little bit about the infrastructure of how clozapine, how large sort of clozapine practices can work. And sometimes you might hear these called clozapine clinics. And what we do at Grady in Atlanta PSTAR is kind of like a clozapine clinic. We see some people who aren't on clozapine, but maybe they've been on clozapine before, or for some reason they can't be on clozapine. So we really sort of focus on clozapine. And we did a survey because not much was known about this in the literature about like, what exactly is a clozapine clinic and can clozapine clinics help with the expansion or more of the appropriate prescribing of clozapine?

**Dr. Rob Cotes:**

So when we surveyed a number of clozapine clinics, the median number of individuals on clozapine was 45. And then often in a clozapine clinic, one of the benefits is having interdisciplinary team around somebody. So this isn't like an act team or anything. This is like within a clozapine clinic, there are different interdisciplinary roles. You can see the disciplines here, psychiatrists, pharmacists, nurses, psychiatric nurse practitioners, case managers, psychiatry residents, social workers, really forming a team around a person who's on clozapine can really be quite helpful.

Okay. What kind of things might clozapine clinics offer? A lot of what they can do is they really do a good job making sure that people continue to get the blood work and making sure that people don't fall through the cracks. Many clinics have onsite phlebotomy. They might have an onsite place where people can pick up medication. So that means somebody goes into the clinic, they get medications, they get the blood work all in the same process. You could understand how in some settings you might go visit with the prescriber, you might then have to go to a lab and then have to go to the pharmacy.

And it's just, people are driving all over town and sometimes this can make it a little bit more centralized and easier to do. But many of these services also have after hours on call service, which I think is really important, because I don't know how many people I talk to on a Friday afternoon or Friday night or on a Saturday or on a Sunday who are like, "Look, I'm having a problem at the pharmacy. I can't get my clozapine." Like that's an emergency and somebody needs to be able to get on that immediately.

Okay. So there's been a number of statewide efforts that have been out there to help increase the use of clozapine. And one of the best ones has been in New York, New York state. And they were actually able to increase the proportion of new outpatient clozapine trials by 40%. And essentially, among all new... 40% sounds pretty good. But just to put that in perspective, for new clozapine starts among all new antipsychotic trials, that number was basically 1.5% and they were able to increase it to 2.1%. So still low, but definitely a very important effort. And you can see some of the things that they did. There's also a North Carolina clozapine network and working on developing one in Georgia as well.

One of the key takeaway points from this talk is that if you or a loved one might be a candidate for clozapine, suggest it to your prescriber. I think this is how stuff gets done. I think the prescribers are really doing the best that they can do, but maybe they're not thinking about clozapine all the time. And if you know somebody, you can be a really, really powerful advocate. And that is exactly what happened back when we were talking about Thomas and the video. His actually it was Dr. Duckworth that advocated to his parents to get the prescriber to think about starting him clozapine. And then there was a big, big shift I think in how he was doing.

So we know that clozapine is underutilized and sometimes it can be really hard to find a clozapine prescriber. And the cure SZ organization does have a map that does highlight some prescribers around the country. Again, another pre-pandemic picture of me, but you can see that those are kind of spread out around the Southeast and there's a lot of clozapine prescribers that aren't actually on this database here. But these are some people that you can reach out to, and perhaps they would have ideas about people who aren't in some of these areas that are covered. Okay. So this is my email address if anybody has any questions. And then there's a lot of additional resources in smiadvisor.org, both on the individuals and families page and on the clinician page and a lot of great information on the NAMI website as well. All right. So we are-

**Dr. Ken Duckworth** (00:50:51):

What a superb, comprehensive and helpful talk. Many of the questions, and there are a lot of questions are answered in your talk. So I want to encourage people to wait a couple days, go to nami.org/asktheexpert. You can find every expert we have, and he did answer a number of the questions that you came up. So let's start at the beginning. A lot of questions on side effects. And so let's just take some of the more common questions. The problem of drooling is known problem that I had with the people that I took care of. I just had them buy 10 pillow cases and just change one every morning. So it wasn't an ongoing source of concern, but then I know there were some medicines that were developed. Can you tell us a little bit about your approach to the problem of drooling?

**Dr. Rob Cotes** (00:51:48):

Yeah. And I think that in the survey we did, not only did over 70% of people say that they experienced drooling, but many of them actually highlight it as a very problematic side of it. So it is a significant issue. And for some people, it can happen throughout the day and then for others, it can and more at night. So there's a number of approaches. You divide them into non-pharmacologic approaches and then pharmacologic approaches. Obviously like having a number of towels can be a helpful thing, especially for people who just have nighttime drooling.

Some people think that sugar free gum might help a little bit. But then there's also some medications that might help. And the number one thing that I often go to is the atropin drops. So these are atropin drops that are often prescribed for the eye, but these don't go in the eye. These goes underneath the tongue. And they go, and they basically absorb into the salivary glands. And what they do is there's been studies that basically show them to decrease the amount of salivary production related to clozapine.

There are other medications that can be used, like for example, glycopyrrolate can be used. Some people might use benzatropine or cogentin. The problem with both glycopyrrolate and benzatropine is that they are anticholinergic medications. And that means that they can cause worsening constipation. They can cause worsening forgetfulness and cognitive issues. And we know that there's been a lot of studies that have been done about anticholinergic medications for people who have schizophrenia and it can really impact their cognition.

So the first line pharmacologic treatment we go to is the atropin drops with actually doesn't, it's not sort of systemically absorbed, so there's none of the constipation impact. There's not the cognitive side effects, cognitive slowing. The other thing that I think is really promising are Botox injections into the salivary glands and into the... that can also really, really make a difference. The Botox might wear off after four to six months. Most psychiatrists wouldn't feel comfortable administering a Botox injection into the salivary glands, but it's very effective treatment and it doesn't have the same sort of systemic side effects that some of the other pharmacologic treatments may have.

**Dr. Ken Duckworth** (00:54:24):

Excellent, important side effect. Great answer. Let's go from the common and distressing to the unusual, but important. Obsessive compulsive disorder symptoms.

**Dr. Rob Cotes** (00:54:36):

Yeah. So there's a couple of different ways you can look at it. Clozapine can kind of do two things. I mean, clozapine can exacerbate people who have obsessive compulsive symptoms already. So like somebody might have obsessive compulsive symptoms and then clozapine might make it worse.

**Dr. Rob Cotes:**

There's also people who take clozapine and it can cause more of a de novo sort of obsessive compulsive type picture. This might happen overall in about 10% of people. It's really understudied, but it can be a really, really big problem. So one of the things that I do first in these approaches is try to figure out, did somebody have obsessive compulsive symptoms before clozapine was started or did the clozapine tend to make it worse? And they is some, it's a little bit unclear, and this is true with any medication is you want the medication to be at the lowest effective dose.

And it's possible that lowering the dose a little bit may help with some of this. It also is possible that early in the clozapine titration, these kind of symptoms may occur. And then there's been some cases of them sort of diminuating over time and getting better. But then once you sort of get out of those considerations, one of the things to do is to try and measure the obsessive compulsive symptoms as well as you can. That way you can kind of track how they're doing over time. Now there's two main approaches, pharmacologic approaches and non-pharmacologic approaches.

So the first thing is to think about before adding any medication, is there a therapist that can help somebody with some of these obsessive compulsive symptoms and do a CBT based approach? Not everybody has an OCD expert in their community. And sometimes the pharmacologic ones are what we have to go to. So often, medications like fluoxetine can be beneficial in these situations. The thing fluoxetine is that sometimes it can increase clozapine levels. So we typically will check clozapine levels and make sure that they are kind of within the same range that we want them to be. Then there's another medication. Well, I guess I'll just sort of leave it at that. But most of the SSRI type medications have been used in these situations, but it kind of is a hit or miss. And I really encourage people to think about like the non-pharmacologic trials and then like on therapy as well.

**Dr. Ken Duckworth** (00:57:13):

I mean, obviously we're not given medical advice here, but you're giving people kind of the comprehensive waterfront of what is out there. Another question is weight gain. Now I've had patients on clozapine and I've had a lot of patients on clozapine tell me that their cognition and thinking is so much clearer, that they're actually better addressed to handle their wellbeing, their self care, their exercise. But as you saw in your slides, weight gain can be a concern. That's the last side of effect I'm probably going to take up, but there was a lot of questions on side effects. So I did want to address that one before we move on.

**Dr. Rob Cotes** (00:57:50):

Yeah. Yeah. I mean, weight gain is a really, really, really big concern. And I think just sort of looking back over my career, I think that the effects of antipsychotic medications and weight gain and cardiac metabolic side effects was one of the things that I think drew me into research and kind of this problem is a really, really serious one. I think a couple of things are important to know about this. The reason that clozapine causes weight gain most likely has to do with its what's called antihistaminic effects. And what that does is it can affect the brain and it kind of, it can affect what's called the satiety point of the brain. So I mean, we eat food and then there's a set of complex signals that tell us that we're full.

But what happens when people take clozapine is that this system becomes somewhat, the system becomes off in some ways and we don't have the same satiety point. And the reason that people gain weight related to clozapine is because they intake more calories often because they don't have that same full sensation. So an understanding of that I think is really key. So sometimes it's important to...

**Dr. Rob Cotes:**

And this is so hard because it really, really stimulates the appetite, but the portion control is really, really important. And you just have to kind of trust that hopefully you will become full.

Now outside of that, the type of diet that people take is really, really important as well as exercise. So it's really, really important to get both sort of the cardiovascular exercise, diet. I think watching sugar, watching high carbohydrate diets might be important as well. I sometimes tell, for people who have gained weight on clozapine, talk about a paleo diet or maybe a ketogenic diet for some individuals.

And then there's some pharmacologic treatments for clozapine as well and antipsychotic induced weight gain. The first one is Metformin. So Metformin is the best studied medication to help ameliorate weight gain for clozapine. And when people start clozapine, I often will offer people starting Metformin at the same time, sort of prophylactically. That's an off-label indication for the use of Metformin, but it's like starting the Metformin at the same time can sometimes help to blunt the weight gain over time.

Now, what we know about the natural history of clozapine and weight gain is that over five years, there tends to be a plateau sort of effect. But it's really, really important to intervene early. Intervene early, and we need to have a stance in our mind that weight gain related to clozapine is unacceptable, and we need to do everything we can to prevent it. There are also newer medications out there. I mean, there's some evidence for a aripiprazole helping with clozapine induced weight gain. Topiramate is one. And then there's the GLP-1 agonists, which I think are quite promising, which include medications like semiglutide. We might be seeing a lot more of that.

**Dr. Ken Duckworth** (01:01:14):

We don't really discuss a lot about off label use, but you mentioned what a great antimanic agent. Allen Green was also one of my teachers when he was at the Massachusetts Mental Health Center. I still think it might be the best antimanic agent. We don't give medical advice here, and it's not FDA approved for that, but it also has remarkable qualities. You want to discuss that because it did come up in the Q&A, and I have seen this personally. This is also for people with Schizoaffective disorder, which has a mood component as well.

**Dr. Rob Cotes** (01:01:50):

Yeah. Well, just as underutilized as clozapine is in the United States, you are much less likely to see it for people who have persistent symptoms of mania and not responding to other medications, unfortunately. So this isn't a big awareness issue. I personally have seen great success for people who have struggled with mania, who've come into the hospital and other times have been on multiple medications. We try clozapine, get it to a therapeutic dose, and then the mania goes away. I think that also sometimes electroconvulsive therapy can be used in these situations. And sometimes for the so-called treatment resistant mania, electroconvulsive therapy is also highly underutilized.

Yeah. I think that actually part of it has to do with, especially in larger cities and bigger sort of metropolitan areas is there's a real... The healthcare system's very fragmented. And a lot of times you don't even know like what has happened in prior inpatient admissions that have just sort of occurred. And there's some attempts to remedy this. I think with various systems like Care Everywhere where you can see sort of more of the historical data. But I just, I think a big part of the problem is people just aren't identifying individuals who have failed multiple trials and are still in a manic episode. Clozapine can just be an invaluable tool.

**Dr. Ken Duckworth** (01:03:19):

Yeah. Couple people have asked the question, I or my loved one is on several antipsychotics. And polypharmacy to me is an indication that things are not going great. How would the actual process be of adding clozapine? Does this have to be done in an inpatient basis? Do you add clozapine slowly, withdraw the medicines? What's your approach? Somebody says the heck with it. I want to go for the most effective treatment. Let's just see what we can do.

**Dr. Rob Cotes** (01:03:49):

Yeah, a great question. And I think that when we, and have looked at trying to develop a system to potentially identify people who might benefit from clozapine, one easy way that you can kind of do it in an electronic medical record is to look at people who are on multiple antipsychotics. That might be a clozapine candidate. So what to do as far as which antipsychotic to back down on first is a question that I get a lot of consults on SMI Advisor about. And typically, the approach that we take in similar situations is the medication that's the most clozapine-like is the one that we tend to back off first. So these are medications like olanzapine or Quetiapine. Fairly sedating medications that have similar chemical structure will typically focus on a similar pharmacodynamic sort of properties. We'll work on those first and then begin to back down some of the other medications later on.

I think one of the challenges is when you're taking someone who's trying multiple antipsychotics onto one antipsychotic, you really have to be mindful that only one antipsychotic is the goal. Because sometimes what happens is things get in the middle of a titration, things somehow there's a change, maybe a change in provider. And then that's just what happens. It's sort of this aborted cross titration kind of thing. So the team really, really needs to be vigilant about trying to go down to just one antipsychotic being clozapine. That said, some people tend to... Sometimes for some people just clozapine is not enough. And adding another antipsychotic can be a reasonable solution perhaps from a side effect management perspective and also from a efficacy standpoint.

**Dr. Ken Duckworth** (01:05:59):

Another question is how long does it take to see effects? I want to give you my window. I had a patient improve on day two. She already had symptom improvement on day two. And I've had people that it took months and months. So now I want to get kind of your estimate of bell curve of the time of-

**Dr. Rob Cotes** (01:06:21):

Yeah. Great question. I think that for time to response, you have to keep the overall response rate into perspective. So you got to sort of estimate that between 40 to 60% of people are going to have a response to clozapine. Then there's been some studies that have suggested that using blood levels of clozapine, so these are done... They're often a send out test. It takes a couple of days to come back. And the reference range, the therapeutic range, sorry, is between 350 to 600 nanograms per mil and sometimes it can be a little bit more. Usually if the clozapine level gets to over 100, sorry, over 1000, then people start to have more side effects and more issues. So typically, we like to have the clozapine level between 350 to 1000 people can respond. As you mentioned, can like at very, very low doses. They don't need to get to three 50. So the way that I think about it is if somebody is still having symptoms and their level is less than 350, we gradually increase the dose to get them to 350. Then if they're at 350, we know that from some research that's been done is that it takes two to three weeks once people have a therapeutic clozapine level to respond. Then sort of on the other side of that, you're really looking at 60 to 90 days on the medication at a therapeutic dose, at a therapeutic level rather to kind of tell if somebody's going to respond or not.

**Dr. Ken Duckworth** (01:08:06):

It is remarkable. This is the one of the very few medicines you can get reliable blood levels. And that is a tool that you can use in your toolbox. Let's talk about the REMS system. The chaos that has ensued from the changes. My understanding is it's currently on pause, but I just wanted to make sure we discussed that.

**Dr. Rob Cotes** (01:08:28):

Yeah. So new clozapine REMS has really had a chaotic rollout. It started in November and there really wasn't a lot of input from the stakeholders, like from the American Psychiatric Association or for NAMI or from other professional organizations when this was rolled out. And I think that a little bit more conversation with the people that used the REM system would've been really beneficial. I'm one of these people who I pull up my internet browser and clozapine REMS is like my homepage. It's like, it's something that I'm in all the time. And some feedback from the users I think might have been helpful in sort of a better rollout of new clozapine REMS.

I think that we're going to talk a little bit about this, about the survey that NAMI has sent out, but if people miss a couple of doses of clozapine, it can cause serious problems. People can have exacerbations and symptoms, people can have, and that sometimes is called rebound psychosis. There's been case reports of people stopping clozapine abruptly and developing catatonia. And that means sort of an inability to move and difficulty talking. So the stakes are really high. The stakes are really, really high.

And I think what I would encourage people to do is make sure you have an open line of communication to your prescriber. That way, if you get stuck at the pharmacy and you can't get the medication, you can talk to somebody and then they can remedy that. They can talk to the pharmacists. I think the pharmacists have been really wonderful in this process and they're understanding, and they understand as well that somebody misses a couple of days of clozapine, things can really... Negative things can happen, but there's been some significant impacts.

And there's a group of professional organizations who are expressing concern about this and who following up with the FDA to try and communicate with them and to give us our feedback about what's working, what's not working and hopefully we can make the system better for people. But as I was mentioning earlier, after 12 months, the risk of severe neutropenia due to clozapine becomes similar to that of other antipsychotics. And I think that there's a real scientific question, if the clozapine REM system, one, is still needed and then two, is it needed after a specific time somebody has taken clozapine where the risk of severe neutropenia really goes down? Ken, sorry-

**Dr. Ken Duckworth** (01:11:28):

Sorry. My internet's a little sketch today. We're going to come back in the survey to the REMS system. Several questions about cognition and negative symptoms. You and I have both seen firsthand it can be transformational in terms of people's experience of voices, delusions. It's quite remarkable for some people, not everyone and we can't predict who. But the question around cognition and negative symptoms, such as motivation came up in several of the question. And I thought, it'd be a great question for you because myself and another person I treasure have different takes on this little controversy.

**Dr. Rob Cotes** (01:12:09):

Yeah.

**Dr. Ken Duckworth** (01:12:10):

You're the referee. You're going to be the tiebreaker.

**Dr. Rob Cotes** (01:12:13):

Yeah. Let me know which side you stand on and then we'll talk. But basically, so it's two sort of separate questions. One is around negative symptoms. Negative symptoms are very, very difficult to treat and medications even clozapine, they can sometimes only have a small impact on negative symptoms. Negative symptoms on the other hand are difficult to quantify. And sometimes people who have negative symptoms actually have untreated positive symptoms. So it's because what appears to be a negative symptom type picture may actually be related to people still having paranoia or sometimes it's related to other social anxiety. So sometimes when people start clozapine with what people thought were negative symptoms actually gets better because of the positive symptoms are now much more successfully treated.

From a medication standpoint, there's no FDA approved treatments for negative symptoms of the illness. There are certain treatments that I think can small differences around the margins. Some of the things that are kind of like antidepressant medications can sometimes help with that. If people have negative symptoms, you have to make sure that they're not actually having a major depressive episode and get people treatment for that. But there are a lot of treatments that have a relatively small effect on negative symptoms.

Now what my experience has been sort of being part of a clozapine program over the last decade is that we specialize in clozapine, but also we've come to specialize in other psychosocial interventions because the negative symptoms can sometimes be enduring as well as the cognitive symptoms. So I think that people often it helps to connect them with other evidence based psychosocial interventions, like CBT for psychosis or CSST or social skills training. So CST is CBT and social skills training combined. Social skills training supported employment. And I think that in a comprehensive program, you really want to offer all of those things to help with the negative symptoms.

Now, cognitive symptoms is another sort of issue. And you know, we talked a little bit about the problem of anticholinergic medications, Benadryl being one of the quintessential examples. So Benadryl and other anticholinergic medications can affect cognition and can affect that can cause other problems that can make people unsteady. They make people constipated. Clozapine actually is highly anticholinergic, but clozapine doesn't cause the same level of cognitive symptoms that you would expect for a medication that's so anticholinergic.

So there's some unique... Clozapine is, I wouldn't say really moves the needle a lot on cognitive symptoms, but clozapine isn't as bad as you expect, is not as bad as you expect for other cognitive symptoms. The key thing is to avoid adding other anticholinergic medications to clozapine and making it worse, like glycopyrrolate or like benzatropine. I see this all the time, somebody's on clozapine and they're on benzatropine. Why? I mean, clozapine is often highly anticholinergic. It contains a lot more of that same compound than just sort of the benzatropine alone.

**Dr. Ken Duckworth** (01:15:46):

I also want to call out the cognitive remediation work, right? This is Kim Muser, Susan McGurk at the Boston university school of psychosocial rehabilitation, just of note. Well, that's all we have time for. I want to say your knowledge is comprehensive. It's fantastic to have you on this critical topic. I'm going to turn it back over to our CEO for the day, Dr. Teri Brister.

**Dr. Teri Brister** (01:16:13):

Okay. Now you've got me nervous, Ken. Thank you so much, Dr. Duckworth and Dr. Cotes. This was amazing. We had one of our largest crowds in a while on this call and almost all of them were still here when we stopped for Q&A. And I think that very much speaks to the importance of the topic. So thank you for that. If you'll go to the next slide, please Dr. Cotes, that would be terrific. All right. You heard both Ken and Rob speaking about the survey. This is something that we've NAMI, as you know, is an advocacy organization and Christina Bott who's the director of healthcare and public safety initiatives at NAMI has been working with a group that includes Dr. Cotes that's focused on the impact of the changes that were made to REMS in November. Even though they were put on hold, we're still actively trying to figure out and help guide the decisions that are made going forward.

So to have something to represent the people that we attempt to speak for, to be your voice, we wanted to get some numbers. And Christina developed this survey. You see the link on the screen, but you also see it in your box. It should have just popped up for you. We'd encourage you, if you have experience with clozapine and specifically with the changes in REMS, for you, if you're a person taking clozapine, if you're a family member or a loved one of someone who's taking it, or if you're a healthcare professional, prescriber pharmacist or a mental health professional, we'd encourage you to fill this out. It'll take you less than two minutes, but just to help us get an idea and be able to represent in conversations with FDA and others about what an impact this is having. So thanks in advance for taking time to do that.

And Ken, I'd like to hand it back over to you now. If Rob, if you will advance the slides. And before we close up, if you can... oh, I'm sorry. Let me cover this one before... No, go ahead, Rob. You were good, but this is upcoming dates that you need to be aware of for NAMI Ask The Expert. April 28th, we have Dr. Tom Insel who was one of the previous NIMH directors, who's going to be talking from his new book, Healing Our Path from Mental Illness to Mental Health on May 26th. We have Rebecca Neusteter who's going to be joining us, talking about criminal justice and healthcare. And now if you'll go to the next slide. There we go, Dr. Duckworth.

**Dr. Ken Duckworth** (01:18:54):

So thank you, Teri. So NAMI's going to have its first book. It's going to come out in September, late September. All proceeds from all royalties, from all editions go to support the mission of NAMI. I've wanted to do this book my whole career, and I'm happy you to say we're ready for it as a society. My colleague, Jordan Miller, who also helps on this webinar and I interviewed 130 people who are using their names and discussing what they've learned, what's made a difference. And whether it's clozapine, being a peer, faith, a job, whatever it is, and whatever combination.

And then we have 35 in America's greatest thinkers and experts answering common questions that I've gotten as the NAMI chief medical officer. And Dr. Cotes is answering the question on how do you think about clozapine? So it gives you an example. This is a practical how to guide. We anticipate it's going to help a lot of people. And I want to say while my name is on the book, it's a total team effort. I just want to make you aware of that. Anytime you come to Ask The Expert, you're going to be subjected to this slide. So I want to apologize if you see it again, because we're kind of proud that we have our first book. So anyway, there it is. Thank you all for that. Terry.

**Dr. Teri Brister** (01:20:17):

Thank you, Ken. And you should be proud of it. I'm proud of it for NAMI and it represents so many of you that are on this call. Some of you probably personally, but others of you will see yourself in it. So super excited about it. If you will go one more slide, Rob, that would be terrific. This will be our last slide. I do want to remind you, we didn't have this listed on a slide. But NAMI's national convention is coming up in June and we would encourage all of you to register for it. It's going to be virtual again this year unfortunately. We made that decision when Omicron was raging wildly across the country, but encourage you to go to nami.org/convention and register. It's June 14th through 16th. And Dr. Cotes is going to be one of our research update centers at the convention. So hope to see you there virtually.

Want to give a final shout out before we close off today, Jordan Miller, who Ken mentioned has been his right hand, literally in the work around the book and capturing stories is the senior producer of the NAMI Ask The Expert webinar series. Other colleagues of ours, help with the effort and make it happen. And one who worked especially hard today was Jessica Walthall who captures your questions for Dr. Duckworth. And I'm looking down at the box right now, 245 questions. We had several pages of questions submitted beforehand from people who had registered. So I think that speaks to the interest concern and a lot of the unknown about clozapine. So huge shout out to Jessica for wrangling those.

Christina Bott again, who developed the survey that we're hoping you're going to take. And Divanna Eckels and Zahira Correa who are two new NAMI staff members in our research team who are joining us for the first time today.

And last but not least, you see our disclaimer here. This series is provided free of charge to participants. Our presenters are fabulous. We've never had anybody say no to us and they do it without an honorarium. So again, I encourage you to think about, if you're interested in donating to NAMI, this is one of the things that your donation would go for. But we thank you for joining us. Thank you for staying with us. And again, Dr. Cotes, thank you so much for joining us and for sharing this information and for your wonderful slides. As a reminder, you're going to be getting a link that include the slides, include a link to the recording, a certificate of participation, and there will also be a link to the clozapine information page on nami.org, which has some downloadable fact sheets there as well. So thank you so much and we hope to see you all again in April. Have a great day.