[MUSIC PLAYING]

K. N. ROY CHENGAPPA: Hello, everyone. My name is Roy Chengappa. I'm going to focus today on clozapine toxicity in the midst of COVID-19 infections. My partner in this presentation is Jane Thomas, who is a nurse manager at Pathways, which is an adult residential facility within our service line. And my name is Roy Chengappa. I am a professor of psychiatry and service line chief for one of the service lines we run at Western Psychiatric Hospital.

And I would like to acknowledge in the next slide Joan, who's recording this presentation; Lori Arbutiski, who's director of behavioral health nursing in sister institution; Dr. Clinebell, a psychiatrist; Dr. Kahn, who's also a psychiatrist; Ms. Kelly Mullen, who's a program manager at our residential facility; and a lot of the nursing and residential staff at our facility.

So in the next slide, we can say that neither Jane nor I have any conflicts of interest to disclose. We've not had any grant funding or sponsorship for this. We've just done it using our own internal resources. The objectives of this CME are to recognize that clozapine is the only medicine to date approved by the FDA for treatment-resistant schizophrenia. Its other indication, which is also a one-off in all of psychiatry-- actually, in all of medicine-- is for people who continue to have suicidal behavior in spite of other efforts to decrease it, and they have a diagnosis of schizophrenia or schizoaffective.

So once people get onto this hard-to-use medicine, the key is, how do we keep them on it, and to understand for this CME in particular the impact of infections on raising clozapine blood levels to potentially toxicity, as well as review the medical and nursing management if clozapine toxicity does occur. And we will use an illustrative case example, which my partner Jane Thomas will describe.

We will also briefly touch on a key point of a recently approved medication, Paxlovid, which is contraindicated when being co-prescribed with clozapine. So the background which is in this slide is something I've already addressed, the-- what it's approved for. The second point is more important. It's very underutilized in the US.

And so when we get people onto clozapine-- really the next slide addresses this-- how do we keep them on it if they've responded modestly, moderately well, or very well? And the common issues in 30 years of use of this medicine, in the clozapine prescribing world, we tend to know quite well, which is severe weight gain, which leads then to insulin resistance, pre-diabetes, full-fledged diabetes, dyslipidemias, sleep apnea, and many medical issues that are related to hypersalivation.

The other thing that we have figured out over time is drug-drug interactions or smoking clozapine interosseous. So we know of medicines used in psychiatry, like Luvox, or fluvoxamine, or antibiotics like Cipro that can elevate clozapine levels to toxicity in a big hurry-- erythromycin as well. And this is not an all-inclusive list.

We also know medicines used in psychiatry and other branches of medicine-- anticonvulsants typically-- or smoking, which a lot of our patients tend to indulge in, can facilitate the metabolism of clozapine and lower its levels. So these are things that we have to be fully aware as medical people and nurses on how to work with people who are getting clozapine.

So since this focus of the CME, as in the next slide, is on infections-- bacterial, viral infections, maybe because of inflammation, because of cytokines-- they can very rapidly shift clozapine from a normal state to an abnormal toxic state, sometimes within a matter of hours. This will be described in much greater detail when we use our illustrative case, so I won't stress on it.

But we've already spoken a little bit to smoking and how that can impact clozapine-- typically lowers it. But then, when you get super sedated, you don't smoke, and it can increase it. And then there is this whole issue in COVID times of hypersalivation and what that means, because if you just aspirate your saliva, as opposed to swallowing it, you could be in an aspiration pneumonia situation, adding to already the ventilatory difficulties that might occur, as we saw when the Delta variant was prominent in COVID.

So the next slide just belabors this fact a little more. Maybe the first point is important here, because we haven't talked a little bit about the CNS consequences of clozapine toxicity. We would typically see it as a prodrome, as myoclonic jerks-- typically in the shoulder area, the facial area, the neck area-- before you have a full-fledged seizure.

So if you're seeing myoclonic jerks, be prepared to very quickly be prepared for a full-fledged seizure and any action items you need to make happen or increase, say, monitoring of that patient you need to undertake. Also, don't forget aspiration pneumonia could easily result. All this could lead to severe morbidity and the unfortunate event of even death. So this is serious business, and we need to pay attention to it, whether it's COVID as respiratory infection, or urinary infection.

So how can we tell whether they're-- it's lethargy that is due to COVID, or vital sign instability that is COVID, or for mental status changes that are much more likely to be clozapine toxic? We'll address this in the next few slides. I'll just touch in the next slide on something we have learned recently from a Swiss study.

The Swiss group used something called the Geneva cocktail, which is a cocktail that probes how the liver functions or doesn't. And when they tested people who were testing positive-- this was more during the delta wave that was sweeping the world of COVID-19-- they noticed suddenly people-- these were not necessarily people taking clozapine.

In fact, there was nobody taking clozapine. These were just general population people taking all sorts of medicines for different medical conditions. They go through the same enzyme systems in the liver. And you can see in red, the 1A2 cytochrome enzyme is blocked over 50%, 3A 23%, and 2C19-- 3A and 2C19 are the minor metabolic pathways for clozapine, but 1A2 is [INAUDIBLE], and that's blocked over half.

You can imagine how quickly that could do things to the clozapine levels. Overnight, literally, you could have this happen, as we will show in our case. And our ability to anticipate this is the reason for our presenting this continuing education. So at this point, I would like to hand off this presentation to describe the case and what nursing interventions are to my colleague and partner, Jane Thomas. Jane--

JANE THOMAS: Our 45-year-old African-American female was discharged from a state hospital and admitted to our long-term residential facility with treatment-resistant schizophrenia. She arrived on clozapine 350 milligrams a day, and she did show a moderate to a good response from her baseline prior to being admitted.

She was also on clonazepam 1 milligram bid and valproate 1,000 milligrams a day for mood stabilization. She developed symptomatic COVID-19, likely the omicron variant. She had chills, fever, and nasal congestion. Within one day, she became markedly sedated. She needed assistance to walk. She was lethargic. She appeared confused. She was bent over while sitting. She was drooling, and she was becoming increasingly-- having difficulty getting her words out.

Next slide, Joan-- nursing interventions continue. Immediately, we-- after looking at our resident, we obtained initial orders for labs. We did a assessment, vital signs, parameters, pulse oximetry, and evaluated her medication regime. We increased communication with the physician. We scheduled calls Q shift after the nurse's assessment was completed and prior to administering any further medication.

We increased our observation to Q 30 minutes from hourly. We encouraged fluids. We offered her cold bottles of water and any drink that she would like every hour. We encouraged her to decrease or stop smoking. We isolated her room. Medications and meals were taken to her. We needed to assist her with ambulation to and from the restroom. We elevated her-- the head of her bed to prevent aspiration on her saliva, and we ensured her oxygen saturation was maintained above 92%.

We also observe for myoclonic jerks or any seizure-like activity, her orientation status, her pulse oxygenation, and her vital signs Q shift for a period of one week. We monitored her room temperature every 30 minutes, and maintained that at 72 degrees. We assisted her with removing heavy-- her coat and other heavy clothing, as she wanted to keep a winter coat on zipped up and was beginning to sweat profusely.

All nursing staff and all staff interfacing with her wore the appropriate PPE, including an N95, a shield, gown, and gloves. We provided the resident with education on COVID-19 and her medication changes. We provided education on handwashing, appropriate wearing of masks, and social distancing. We administered and held medications per the physician's order. Clozapine was decreased to 200 milligrams at bedtime, clonazepam 1 milligram in the morning was discontinued, and we did maintain her valproate at 1,000 milligrams daily.

K. N. ROY CHENGAPPA: Thank you, Jane. This is very illustrative of the immediate actions that had to be taken. And one of the reasons for doing this in house, as opposed to shipping it out to an acute care facility-- this was during that omicron surge in January of '22, when people were waiting in all our urgent care, ER facilities for hours on end.

And so they were telling us to keep people where we could monitor them closely, such as our facility, and send them if they were getting beyond a certain stage. For instance, if the oxygen dropped to less than 90, we would be worried. Or if she was in breathing difficulty or her vitals sign instability got to the point that we could not manage her, we would have to ship her out.

What would a physician do under such circumstances? We would simply need very quickly to cut the dose of clozapine in half at least. This is the consensus statement. There's no empirical evidence to say half is the best, but it's a start. In some instances, you may just have to cut it out even.

But we cut it in this instance from 350 to 200, and we were able to monitor her every 30 minutes, as Jane pointed out. We were keeping an eye on her pulse ox, and vitals, and mental state, so we had a little more comfort, as opposed to a setting that might not have that ability. And remember, trying to just wait for blood levels-- unless you have close to point of care testing, it's going to take two to three days.

There are facilities anymore in the country that can get it back in a few hours, but the one that we are working in still takes two to three days to get the results back, So we clearly could not wait for those blood levels. And if you did cut it back, and if you had fast turnaround of blood levels, it might help you actually and guide you on tapering, rather than cold turkey stopping.

Communication is critical in this business-- maybe once a day, maybe three times a day, just depending on what's possible-- between nurses, physicians being prepped to send them out to acute care facilities is critical, and watching for cholinergic rebound. With such a highly anticholinergic drug, the opposite could happen. So a cholinergic rebound especially would present often as an altered mental state, diarrhea typically, and what might look to many people, quote, unquote, as an "organic" mental state. And this can confound the clozapine toxicity and the COVID-19 picture, so just be prepared for that. So at this point, I'd like to hand off back to Jane.

JANE THOMAS: It's very important-- a nurse should know many things regarding patients in different settings and with COVID-19. First, we must be knowledgeable of the symptoms of COVID-19-- especially the different variants that are appearing. We need to be knowledgeable of the symptoms of clozapine toxicity so we can quickly intervene.

We need to understand the effects any type of underlying infection may have on clozapine levels; understanding drug-to-drug interosseous that may occur with clozapine; be willing to communicate with your attending physician immediately, depending on mental status, vitals, pulse oxygenation concerns, or the need to transfer to a medical facility; and be knowledgeable that Paxlovid, which has recently been approved by the FDA under emergency use authorization for mild to moderate COVID-19, is contraindicated in clozapine treated patients.

It's also important to know that African-Americans may have readings of 1.5% lower than their white counterparts. For example, a pulse oxygenation reading of 92% may actually be 90.5%, demanding a more rapid intervention, such as transferring to an acute care facility.

What should a nurse know and do? In an ambulatory setting, calling 911 and having the patient transferred to a general medical hospital must happen if seizure activity occurs, if severe breathing difficulties are noted, if the pulse ox falls below 90%, if you note profuse sweating, any signs of physical distress, if the patient becomes rapidly delirious and/or extremely sedated.

It's also important to always send the current medication list, recent vitals, pulse oxygenation measures, and provide the ED doctors and nurses with a verbal report that includes the patient is on clozapine and we are suspecting clozapine toxicity in the context of an infection or COVID-19. Don't hesitate to communicate your observations, your assessment, and your concerns with the physician. It is most important that we act rapidly.

K. N. ROY CHENGAPPA: So should I do this part, Jane, or are you going-- or, no, you go ahead, because I think it's still sort of a good flow.

JANE THOMAS: OK.

K. N. ROY CHENGAPPA: Yeah.

JANE THOMAS: So how did our patient do? Within one to two days of cutting the clozapine from 350 to 200 milligrams, she was alert, she was oriented, and able to walk on her own. Her vitals and her mild hypoxemia normalized shortly thereafter. We did obtain clozapine levels, and as shown in the next slide, during clozapine toxicity, the level was above 1,000--

K. N. ROY CHENGAPPA: Nanogram, nanogram--

JANE THOMAS: --nanograms grams per milliliter, in spite of her continued smoking, but came back down when the dose was cut. We also cut the pre-existing clonazepam in half, 1 milligram bid to 1 milligram per day. We left the pre-existing valproate 1,000 milligrams per day alone in view of the potential for seizures with clozapine toxicity, which did not occur in this instance.

K. N. ROY CHENGAPPA: So I can speak to this issue. And just to orient the people who are listening in and watching the slides-- so the first column is pre-COVID, three to four weeks. This included the period before she came into our facility. She didn't, obviously, have COVID, and she didn't have COVID toxicity. In fact, she was very alert, even during this asymptomatic phase, which is the next column, where we didn't see symptoms of COVID or of clozapine toxicity.

Within a day or so of the six-day period-- a day and a half maybe-- when she developed chills, fever, nasal congestion, we saw what we have outlined in red-- very sedated, needed support walking. And as Jane was pointing out earlier, even her words couldn't be fully understood. So she went from someone who was alert and very normal looking all the way to this extreme picture.

So I think that's what we need to be alert to. And certainly, this could be COVID infection, but this is clozapine toxicity. And that's a little different from COVID infection. So it's something to keep in mind, that the clozapine levels have built up rapidly. And then, once you cut the dose in half, everything seems to come down fairly quickly, as the next slide will show when we look at the vital sign parameters.

I'm just concentrating on this ellipse here, which shows a blood pressure began to fluctuate from a normal pulse rate-- she was tachycardic to begin with-- went even higher. And she dropped into the low 90s. In fact, at that time, we did not have knowledge about racial differences in the oxygen concentration using pulse ox. We read this in the literature as we were writing it up, and we realized she's very close to the borderline of 90, if we were to take an average of 1.5%, as Jane had just pointed out.

Her temperature also moved into a worrying range, but as she-- within a day of cutting, as you will see in the next slide-- she was high to begin with. Look at her blood levels, already above 800. In the asymptomatic phase, she's already beginning a slow rise, it appears. And then, within days until we cut it-- we cut it almost in a day and a half of her showing these signs and symptoms of clozapine toxicity-- she became much more alert. And the blood levels dropped, and they were in the much more reasonable range that we are used to with clozapine, in the 400s.

The last point I want to make about this-- and I won't belabor this-- is Paxlovid, which is the brand name for this agent, has received emergency use authorization. It's a combination drug of two protease inhibitors-- nirmatrelvir and ritonavir. Ritonavir's been around since HIV days, and still used. And its whole job in this combination is to boost the levels of nirmatrelvir, which acts against the spike protein of COVID, or the coronavirus.

But in doing so, it blocks 3A, which is one of the minor metabolic parts for clozapine and many other psychiatric drugs, including Lurasidone and pimozide. And this could elevate, certainly, clozapine to toxic levels. So I'm not going to belabor this. We have a separate 30-minute CME that's being worked on currently. But this is something to in the context of what we just said about clozapine toxicity in the midst of a COVID infection.

And this is a drug that could potentially be added and give you, if you like, a double whammy. So certainly, it's something for the audience to be aware-- Paxlovid is contraindicated in people who are taking clozapine.

So the next slide is essentially references, which-- we didn't clutter up our earlier slides. They're here. There's even more resources. If you want to reach out to us, you certainly can. And with this, we finish our formal presentation, and we will just go through some question/answer sessions at this point.

And I'm going to reach out to Jane and ask a straightforward question. What would the nurses need to know by way of knowledge? What would they look for in what to do? And what would they action, depending on what's happening as they are monitoring a patient who is on clozapine and suddenly experiencing symptomatic COVID?

JANE THOMAS: I think, most importantly, it is very important for the nurse to know her patient and know their baseline. That way, when there's any variation, they realize that this is not the norm. You must be aware of clozapine and the impact it can have on a patient who smokes, who develops an infection such as COVID. Be aware for the symptoms that you may see outwardly, such as what we saw was the marked sedation, her difficulty in speaking, in ambulating, the excessive drooling-- just the marked change, because we had gotten to know her for a few days and knew what her baseline was.

K. N. ROY CHENGAPPA: That's critical, I think, Jane. I think you've pointed it out. What about the vital sign changes that we concentrated on?

JANE THOMAS: We certainly need to be aware of blood pressure dropping. Pulse rising could indicate that she's becoming dehydrated-- or the infection itself. The pulse ox is very, very important, because as we pointed out earlier, for African-American, it could be 1.5% less. So she was already running low at 92, and we needed to realize that could have really been a 90, or maybe a 91.

And what would we do? We would want to do a much more thorough assessment of her vital signs, of her mentation, elevate her head of the bed so she does not choke on any of her saliva, and absolutely reach out to the attending physician immediately with our findings.

K. N. ROY CHENGAPPA: One of the questions I've heard since we've talked about this patient to our colleagues-- and even the nurses have asked-- what would help us distinguish COVID-19, which sometimes has very similar features when it affects the brain, versus clozapine toxicity? So what would you teach nurses to look for when it comes to COVID symptoms versus clozapine toxicity, given that the two might have some overlap?

JANE THOMAS: I think that it's very important to understand that clozapine toxicity is-- I think presents a much stronger visible case of symptomology. The COVID-19 can often been confused with allergies, or colds, or maybe an upper respiratory infection, but with the clozapine toxicity, you're definitely going to see the symptoms of excessive sedation, lethargy, change in mental status, the excessive drooling, difficulty walking, maybe getting words out that you might not see at the start of a COVID-19 infection.

K. N. ROY CHENGAPPA: Absolutely. And I think that's-- those are the key things to keep in mind. Know and even though COVID sometimes can be rapid in its own symptoms, and even if there's loss of taste-- that typically doesn't occur with Clozapine toxicity-- or loss of sense of smell, the older COVID surge symptoms-- some of that may recur with even these variants, all this runny nose, chills, and fever. That's a little different from clozapine toxicity. I think you brought those things out really well.

And the need to transfer-- we had a situation where we have 24/7 nursing in an adult residential facility. What about if I was working in a group home and we had, say, a nurse only part of the day? And so when she's signing off or he's signing off to someone else who may not be trained as a nurse, what would their responsibilities be if they have like four clozapine patient in that group home of, say, 16?

JANE THOMAS: I think education is key, and making sure that people in other settings, if they're non-professional nurses, have an understanding of what clozapine toxicity symptoms are, and that they're looking for those very closely, because that does require an immediate intervention, whereas perhaps COVID is something that separately could be managed, where clozapine toxicity demands physician and medical intervention.

K. N. ROY CHENGAPPA: Yeah, I agree. And so that's, I think, the absolute key. And now that we know Paxlovid is contraindicated, but it's really approved more for community use-- and it's possible most of the docs in the emergency room anymore would be wised up to the contraindications of Paxlovid, which are quite a few. We concentrate on psychiatric drugs, which include clozapine, Latuda-- or lurasidone-- and pimozide. But there's a whole bunch of drugs used in medicine that are contraindicated.

But I think, in a nurse-to-nurse or a nurse-to-physician transfer, maybe just worth pointing out the patient is on clozapine so Paxlovid is contraindicated-- maybe just worth saying that one sentence in the direct phone-to-fund transfer--

JANE THOMAS: OK. Yes, that's very important. It's always important to call the emergency room ahead and let them know that you're admitting-- a patient with a psychiatric illness is s to the emergency room. It might require some special care regardless, and even more important that we're suspecting clozapine toxicity. That's very important, how they're-- the doctor and the ED will formulate the plan of care.

K. N. ROY CHENGAPPA: Yeah. Thank you, Jane. And from my perspective, I think, if I had to give an-- if I had to give two or three bottom line messages to docs, it would be don't wait for the clozapine level. Act immediately if you suspect clozapine toxicity. Cut the dose, whatever that percentage. 50 is a general guideline. But if you need to cut it out, cut it more than 50%, cut it slightly less, but cut the dose.

And see if the mental status improves rapidly. You should see it improve fairly rapidly, as we did in our patient. So that would be my message to docs. But otherwise, thank you so much for being a fantastic partner in this, Jane. And I hope the audience will benefit from this education and CME. So--

JANE THOMAS: Thank you.

K. N. ROY CHENGAPPA: --thank you.