

[MUSIC PLAYING]

KN ROY Good morning, everyone. Welcome to part 2 of this continuing medical education series. The first one we did on
CHENGAPPA: this issue was to talk about COVID and what it does to the hepatic cytochrome enzymes.

And in this one, we've titled this presentation the contraindication for using Nirmatrelvir and Ritonavir, more popularly known as back Paxlovid, that has been marketed and advertised recently for preventing mild to moderate COVID illness from progressing to severe illness and hospitalization.

Up until three weeks ago, it was a contraindicated medication Clozapine and Paxlovid. We have just learned that three weeks ago it was revised to be used with precaution. Nonetheless, as you will hear in this continuing education, we would still suggest very careful consideration of combining Paxlovid with Clozapine, for reasons you will see why. Next slide.

I have my co-presenters, who you might be able to see in this recording. Dr. Yabs, Melanie Yabs is a clinical pharmacist. You can see her degrees. And she is here in our service line, serving as a clinical pharmacist, a huge resource for us, And part of the Department of Psychiatry and Pharmacy at UPMC's Western Psychiatric Hospital.

And Joe Zimmerman, who is recent and maybe not so recent director of quality and patient safety, who's landed with his feet running as part of UPMC's Western Psychiatric Hospital system.

I have been here for 30-plus years. And I have an appointment at the School of Medicine in the Department of Psychiatry as a professor. And my administrative role here is as service chief of the CRS service line of UPMC's Western Psychiatric Hospital system. So to the next slide--

We have no conflicts of interest to disclose with this presentation. The next-- So our three main objectives-- the first one will be described by Dr. Yabs, which is the mechanism of action of Paxlovid.

The second is to describe and try and recall in this presentation, or perhaps by looking at this PowerPoint later or the references, of those interactions of concern, including contraindications between Paxlovid and certain antipsychotic medications.

And Joe Zimmerman will bring forth to us the pragmatic clinical indications and considerations of situations where a patient might be prescribed both Clozapine and Paxlovid, and the issues that could result. And so to the next slide--

OK, so what I would like to talk about here in two sentences, if we could go back one, is what COVID does to the liver, so what COVID does in moderate to severe illness.

This is based on a Swiss study which looked at a small number of patients, none of whom were on Clozapine, that it blocks what we call the cytochrome 1A2, 3A4, and 2C19.

These are major metabolic pathways for a lot of psych medicines. And in fact, 1A2 is the major pathway for the metabolism of Clozapine. So without even Paxlovid in the mix, we reported this case from February of 2022 of how toxic she became on Clozapine once she developed COVID 19. And her illness was seen as mild to moderate, not severe. So this sort of woke us up. And we found the Swiss study in the literature.

The next slide refers to Paxlovid receiving emergency use authorization by the FDA. And the patient who receives Clozapine in our Clozapine clinic here, his mother called us about Paxlovid and wondered if I or his family doctor could prescribe this because he was having a case of mild to moderate COVID in the community. And she was a little worried about him progressing to a serious illness, for which this drug has been approved under this EUA by the FDA.

At that point, we still had an absolute contraindication for the use of Clozapine. And so we began a process by which we began to disseminate this information to doctors, advanced practice providers, and anyone else who was interested in this, pharmacists, on what would be a major patient safety issue.

And so this essentially has led to our discussion this morning or to the previous CME on what Clozapine and COVID have in common, that is what we call the two hit theory. So the next slide--

So in this effort, the checkboxes are what we've already done. We've sent out a short, succinct slide set to physicians and advanced practice providers in Western Psychiatric Hospital and in the larger Western Behavioral Health Network. We published a letter to the editor in *Schizophrenia Research* of the case that prompted some of this thinking.

We have completed-- and the link here and in the reference slide will discuss what COVID can do to the liver and elevate Clozapine levels. We have also reached out to our large Clozapine clinic here locally of nearly 170 patients receiving Clozapine, to them and to their caregivers, talking of our concern.

We have also published what is considered a TIP, published nationally in the *SMI Adviser*, maintained by the American Psychiatric Association. And that was vetted by the experts at the Clozapine Center of Excellence, which is a national group. And we've begun notifying-- nearly 80% of 170 patients have been notified.

Today is the contraindication, and as of three weeks ago a precaution of using Clozapine with Paxlovid. And this may be my last slide before I hand off to Dr. Yabs to talk about this issue. So Dr. Yabs--

MELANIE YABS: Thank you so much. So as the pharmacist here, my portion will focus mainly on Paxlovid and discussing the medication more. Next slide.

So Paxlovid is a combination medication. It's made of two meds, Nirmatrelvir and Ritonavir. Nirmatrelvir is a sars-cov-2 main protease inhibitor. And so what this means is a protease, it's an enzyme that's very crucial to viral replication.

So what Nirmatrelvir does is it inhibits or it blocks this enzyme from helping the COVID virus replicate. And then we have Ritonavir, which is FDA approved as an HIV-1 protease inhibitor. So this is typically prescribed for HIV treatment.

However, when it's used in combination with another protease inhibitor, its function is to boost or enhance the effect of the other medication. So what it does in this situation is it enhances the effect of Nirmatrelvir in preventing that viral replication of the virus.

So it does this by way of something called CYP3A4 inhibition. CYP3A4 is an enzyme that metabolizes Nirmatrelvir. So by inhibiting that metabolism, Ritonavir allows Nirmatrelvir to last longer in someone's system and work longer in someone's system.

And so Paxlovid, these medications, the Ritonavir pills and the Nirmatrelvir pills should be taken together as prescribed in order for it to work well. Next slide.

So who is Paxlovid indicated for? Who can it be prescribed for? So Paxlovid is authorized for use in those with mild to moderate COVID 19 in adults and children 12 years of age and older. And they have to be at least 40 kilograms or 88 pounds. They have to have a positive test for the virus. And they have to be at high risk for progression to severe COVID 19, including hospitalization or death.

So these patients-- so Paxlovid should not be prescribed for pre-exposure prophylaxis if a patient thinks there's a chance of them being exposed to COVID. It should not be prescribed for post-exposure prophylaxis if someone has been exposed but hasn't had a positive test yet. And it's also not indicated for initiation for a patient that has been hospitalized with severe COVID.

All right, next slide. All right, so on the left, this is what normal viral replication looks like. So there's an important step called proteolysis, where the enzyme or the protease cleaves the long viral genetic material into smaller fragments. And so this is very crucial to viral replication.

But on the right, as you can see, Nirmatrelvir blocks this enzyme. So it blocks this step from occurring. And the viral genetic material cannot be cleaved. And so therefore viral replication cannot occur.

So that's how Nirmatrelvir works. And as I said before, Ritonavir is there to boost this effect, enhance it, and make Nirmatrelvir last longer and work longer in one system. Next slide.

So Paxlovid should be given or administered twice daily. There's a morning dose and then evening dose. So one dose consists of one tablet of Ritonavir 100 milligrams, and two tablets of Nirmatrelvir 150 milligrams. So all three tablets should be taken at the same time.

And a full course of Paxlovid lasts five days. So it should be taken five days in a row, no interruptions in the course, just like with antibiotics or other medications.

With Paxlovid, there were some phase 2, phase 3 trials that showed that it should be taken within five days of symptom onset. So it should be prescribed as soon as possible after the high risk patient tests positive for COVID.

These trials, though, showed that when patients were given Paxlovid within three days of symptom onset, hospitalisations and deaths were reduced by about 89%. So it's pretty significant. Next slide.

So this is a list from the package insert of the contraindicated medications that should not be used with Paxlovid. So at the time that this was made, the antipsychotics of note were Lurasidone, Pimozide, and Clozapine.

As Dr. Chengappa had noted in the beginning, there has been a recent revision to that. And I'll explain as Clozapine has been removed from the contraindicated list. But there's still precautions to be taken when administering both Paxlovid and Clozapine.

So this is part of the list-- next slide-- and so this is the other half of the list. As you can note, there are several medications. All of these medications are contraindicated because of their use with or because of their metabolism with the CYP3A4 enzyme, which Ritonavir also uses.

So there's competition there with these medications using that same enzyme. And because these medications, if they're used with Paxlovid, it that can cause an increase or decrease in levels of either these medications or of Paxlovid, causing one or the other to be either toxic in the patient or ineffective.

So it's important to note that there are several drug-drug interactions with Paxlovid in general. And providers should be aware of this and can take a closer look in the package insert.

On this slide, of note for those in a psych practice like us, we have some sedatives and hypnotics, like Triazolam and oral Midazolam that are contraindicated with Paxlovid. Next slide.

So here we'll take a closer look of using Paxlovid with antipsychotics. So at the time, Quetiapine-- Quetiapine and Paxlovid, you should be cautious when using these together because the effect on the concentration of Quetiapine is that Paxlovid can increase Quetiapine levels in a patient.

What's recommended here is that the Quetiapine dose is reduced and the patient is monitored for Quetiapine-associated adverse reactions, such as hypotension or sedation.

And then down below, we have the contraindications, with Lurasidone Pimozide, and at the time, Clozapine, where these three medications are contraindicated due to the effect of Paxlovid on them. So Paxlovid can increase the concentration of Lurasidone, Pimozide, and Clozapine.

And the reason for this is coadministration is contraindicated due to serious and/or life threatening reactions, such as cardiac arrhythmias. So with Lurasidone and Pimozide, these two medications are associated with QTC prolongation. And with increased levels, that definitely increases risk of cardiac arrhythmias.

With Clozapine, it was contraindicated at the time. Now it has been changed to a precaution similar to that of Quetiapine, where coadministration is allowed, however you definitely need to monitor for adverse effects because they can be serious and fatal with Clozapine toxicity, such as myocarditis or seizures. So it's important to note that as well.

And next, I'll send it to Joe to talk about clinical considerations with Paxlovid and Clozapine.

JOE
ZIMMERMAN: Thank you, Melanie. And as I move into my first slide, I just want us to paint the picture and think about our patient population that will be caring for. And so it's really important to think about the patients from both a medical, physical medical history, as well as a psychiatric or behavioral history.

And this is really important because our mental health conditions can increase the risk and severity of COVID 19. As Melanie discussed the clinical indications of when we would prescribe Paxlovid, Dr. Chengappa also talked about the one-two punch.

And so what we're thinking about there is that initially when a patient develops COVID 19, that is the first punch. The second punch would be potentially the prescription of Paxlovid. And those together would increase some of the components that I'll be talking about next. But it's really important for us to take that into consideration.

Also, we have to recognize that these prescriptions may be coming through, not only primary care physicians, as well as other providers on an outpatient basis, and most recently, on an inpatient basis as well. And so our patients may be presenting to our ambulatory clinics as well as our emergency departments in addition to our inpatient units.

As we move on to the next slide, we'll see that if there is a patient that presents with a prescription for Paxlovid and they also have Clozapine as well as the antipsychotics that Melanie discussed, some of the findings would be the cardiac arrhythmias. We would potentially see decreased oxygen oxygenation.

One thing to note around the decreased oxygenation is we know that there is a higher likelihood of being diagnosed with a psychiatric disorder or diagnoses, I should say, for our people of color. And with that also, our pulse oximetry that we currently utilize does not adequately capture that in a way that would be similar to our white or non people of color.

So we would anticipate there would be potentially a few percentage points difference. And so for a quick example, a white individual may present, and it may show 94% oxygenation and be relatively close to the accurate recognition. Whereas a person of color, it may show 94%, but truly be 91%.

And so we need to take that into consideration when we see our patients and evaluate them and triage them. Also, given the one-two punch, it is known that the Clozapine levels will not only increase during the COVID infection and illness, but also with the utilization of Paxlovid.

And so we may see seizures, myoclonus, hyperthermia, and then sedation as well. And so if that cannot be identified of why we're seeing some of those, we would strongly encourage you to think about the interactions that Clozapine is having or Paxlovid is having with our Clozapine levels.

And so as we move into the next slide, we see one of our recommendations would be to consider reducing the Clozapine dosage as quickly as possible. And just as Melanie talked about, this is going to be some-- Paxlovid will be a medication that's prescribed to our patients, hopefully within the first five days of onset of a mild COVID 19.

We would also want to talk to our patients about the fact that Paxlovid is not the only approved treatment for mild to moderate COVID 19. So I can imagine it would be anxiety provoking or challenging for some of our patients that are prescribed Clozapine or other antipsychotics to know that one of the more widely marketed medications out there, Paxlovid-- it may appear that it's only treatment approved. But that is not true.

Some of the other alternative therapies for COVID 19-- we have a monoclonal antibody, and we have multiple antivirals. And one of the antivirals that I want to just bring to our attention is Remdesivir. That also has a CYP3A4 pathway. And so it may have an impact.

So just as we're talking about the importance of thinking about Paxlovid and the prescription of that, I would also caution around Remdesivir and thinking about the pathways that it would take as well.

And so as we move on, I want to open it up to some dialogue as we talk about points of discussion and maybe some questions that you may frequently see or interact with our providers. So Dr. Chengappa, I'm going to turn it over to you.

KN ROY Thank you, Melanie and Joe. I think it was very well put together, and sort of flowed beautifully. I think we've had
CHENGAPPA: a preliminary discussion this morning, given that the package insert for the emergency use authorization has shifted from a contraindication to a precaution.

But I would sort of argue-- and I don't know what your thoughts are-- on us being doubly careful, given Joe pointed out the one-two punch. That's a critical piece to remember because even though the Swiss study was in moderately severe and hospitalized patients, we could easily see those effects in the community.

And it's not that every patient who's receiving Clozapine and gets COVID is going to be in that situation. But certainly it's a hard enough drug to get people on. It's the only approved drug for treatment resistant schizophrenia. It's way underutilized.

So this one-two punch does worry me, even though the package insert has been revised in favor of use. So that's one thought I have. But I'll leave it open to the two of you to comment.

MELANIE YABS: Yeah, I think it's very crucial to remember that not just COVID 19, but any infection can increase the levels of Clozapine itself. So with that, even like UTI or just any sort of infection, some sort of inflammation-- so that, on top of using Paxlovid, the levels can get extremely high. So even though it's not contraindication anymore, we do need to take extreme precaution for sure.

JOE Yeah, well said, Melanie. I think we just need to understand that within treating our patients that there is going to
ZIMMERMAN: be multiple factors that influence their outcome. And so with a wide variety of presentations, given seizures as well as sedation, decrease oxygenation, which could also be part of the COVID 19 progression, as we would have to strongly consider whether the drug-to-drug interactions that are potentially happening as well.

KN ROY And the other point I think that both of you have brought up, but from a very practical perspective, we know this
CHENGAPPA: just working in the front lines. Clozapine, typically in terms of getting blood levels to guide our dosing, often if it's sent to specialty labs, are going to take days and days to return.

We have to act fast. Our case report, in fact, we cut it. And instantaneously, when we saw the patient not just experiencing mild COVID, with chills, fever, and rigor, but she was clearly neurologically impaired.

And so we had to act instantaneously by cutting a dose close to half of what she was receiving. And within a day, we began to see the clearing of that. I mean, sure, someone would argue that a point of care test for obtaining Clozapine levels. But that's not uniformly and widely and broadly available to everyone. So that's another point I think that this audience might be interested in hearing.

I don't know what your thoughts are on that list of contraindicated meds. There's a whole bunch of meds that some of our patients might be on, Melanie, because typically comorbidities, especially medical comorbidities, not just the metabolic syndrome or weight gain related, they have a whole bunch of comorbidities, even when they're young. What your thoughts are on that?

MELANIE YABS: Yeah, so it's important for all providers to be aware of these drug-drug interactions and to take a close look at what's recommended.

And it's not always that Paxlovid will cause toxicity of these other medications. Some of these medications might cause the levels of Paxlovid to be too low to be effective. So it's important to understand the risks and benefits of using some of these other medical meds with Paxlovid because you don't want to prescribe Paxlovid if they're on something that's going to make it ineffective.

So it's important to see exactly what the interaction is with some of these medications for all prescribers because all sorts of meds interact with it.

KN ROY

CHENGAPPA:

I think this brings up a good point about the flux in these public health emergencies. I think it's-- the three of us, we've talked about this in the discussion leading up to the CME, of we have to be very aware that it was contraindicated three weeks ago. It was revised.

But we still know of this one-two punch. And so we still have to be super careful. And I don't know what your thoughts are on that, Joe, as well as on the EMR. Some of them warn you on the spot, stop you almost as you're writing the prescription electronically. Others don't really even talk about it because of this rapid use in a public health emergency, you can see the benefits of that.

But you can see the negatives of not everyone knowing everything. So the dissemination piece is a little held back.

JOE

ZIMMERMAN:

Yeah, so it's really important for, such as this medication, which is under emergency use authorization. And so it's great to see that we have therapies out there to be able to support our patients.

Unfortunately at times, though, our systems do not have time to support our providers in making sure that we are getting this information in front of patients, as well as preventing any adverse events from happening.

And so the system I'm specifically talking about is the way that we prescribe and fulfill our medications. And so there is central databases that would help support and potentially utilize triggers to notify providers when there is a contraindication or consideration that they should take into consideration.

However, we also know that the alert systems are not the most effective. And so alerts can be overridden. Or they just might not be effectively designed, or potentially might not all align with the current contraindications. And so some systems may actually have the contraindications built in. And some systems might not be up to date with that as well.

And so I think that, really, the thing that excites me most about being able to share this knowledge with each of you is the fact that this is how we provide support to our clinicians in making sure that they have the expertise to be making those decision making skills and have the autonomy to know what they can and what they should consider prescribing because our systems have yet to be able to support them the best.

So I would just take that into consideration that we have a lot of failure modes in place, especially within filling medications. But with an emergency use authorization, it does take a little bit more time for those systems to get in place.

KN ROY

CHENGAPPA:

Thank you. So thank you both. I think what we can leave the participants of the CME with is a reference slide, deliberately not to crowd the slides with an excessive amount of references and the constantly changing information that we all get.

And some of us may be able to keep up with this information for others. You would want to disseminate it as we are. We will put in a reference slide that we'll talk about COVID and its impact on the hepatic cytochrome, the first punch. And then we will also give you the two package insert guidance documents from when it was contraindicated until three weeks ago. And as Melanie was pointing out, it's now a precaution.

And then we'll also give you information on the national online publications that the Clozapine Center of Excellence that's maintained by the American Psychiatric Association, the tips, as they call their publications, on both these issues COVID and Clozapine toxicity or the potential for Clozapine toxicity, and Paxlovid, and the concerns about using that in this population, and a couple of other references that might be of use.

But otherwise, I thank you both for this presentation. And I hope you as an audience find this useful and helpful in your practice. Thank you, everyone.

JOE Thank you.

ZIMMERMAN:

MELANIE YABS: Thank you.