



Developing Written Educational Materials for Patients on the Effects of COVID-19 Infection and Paxlovid Use on Clozapine Levels

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Panel

Elizabeth Kistler, MD

Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine
Comprehensive Recovery Services, Western Psychiatric Hospital, UPMC

Maribel Piechowicz, MD

PGY4 Resident, Western Psychiatric Hospital, UPMC

Patrick Frailey, MD

PGY4 Resident, Western Psychiatric Hospital, UPMC

Disclosures

None of the panel members have any conflicts of interest to disclose in connection with this presentation.

Learning Objectives

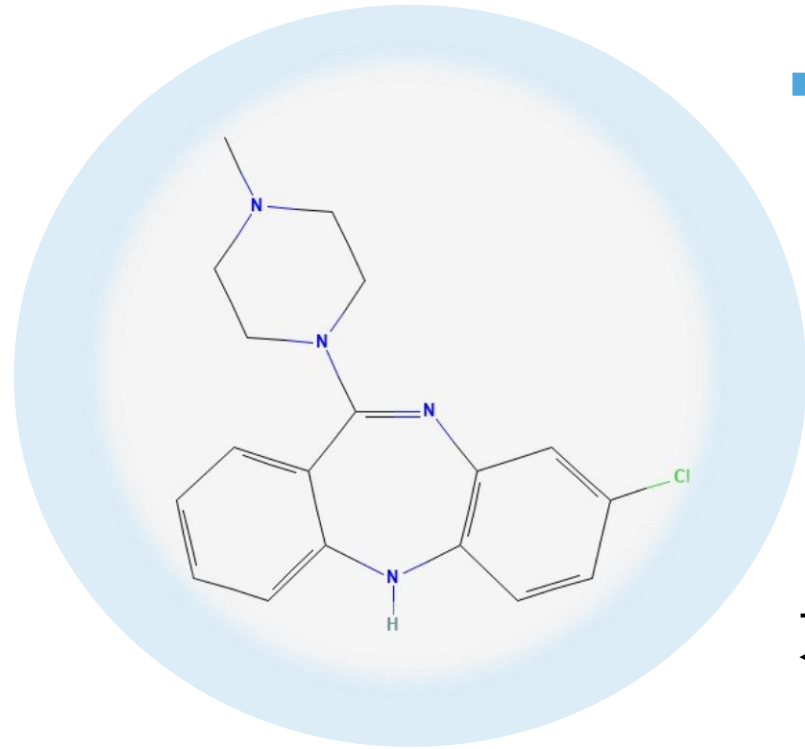
1. Review the potential concerns related to COVID-19 infection, Paxlovid treatment and risk of clozapine toxicity.
2. Recognize the potential barriers in creating effective written educational materials for patients.
3. Understand methods for creating and evaluating written educational materials for patients.

Background: Clozapine, COVID-19 and Paxlovid

Elizabeth Kistler, MD

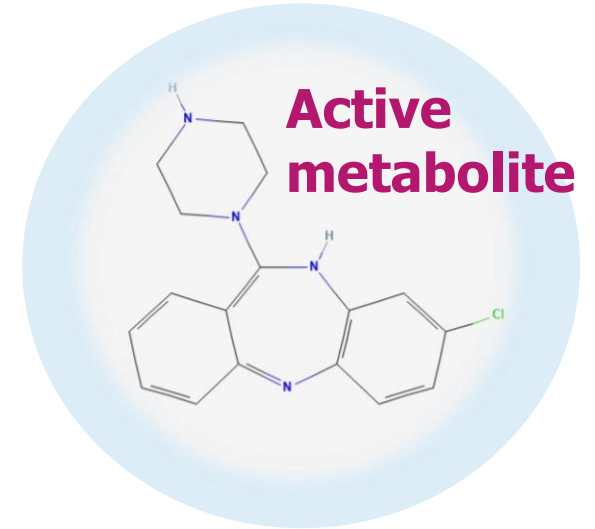
Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine
Comprehensive Recovery Services, Western Psychiatric Hospital, UPMC

Clozapine Metabolism

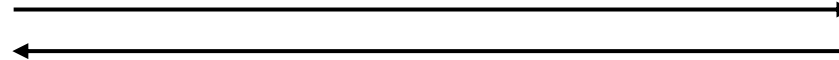


Clozapine

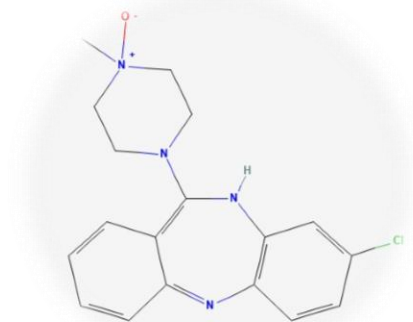
CYP 1A2
CYP 2C19
CYP 3A4
CYP 2C9
CYP 2D6



n-desmethylozapine
(Norclozapine)

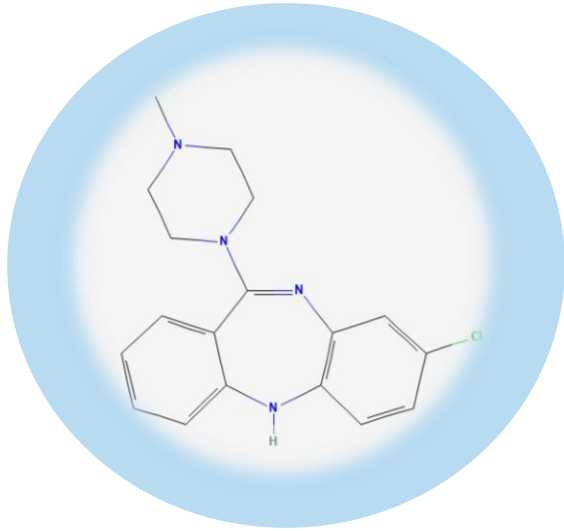


CYP 3A4



clozapine n-oxide

Clozapine Metabolism: Infection



Clozapine

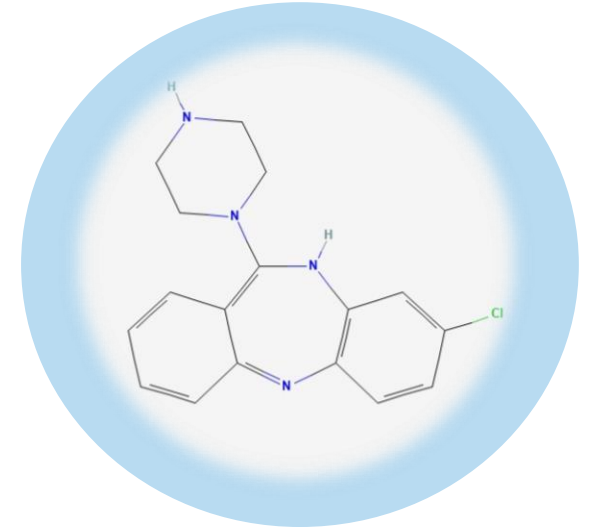
CYP 1A2

- Major metabolic pathway
- Infection is a **STRONG INHIBITOR**
- Inflammatory cytokines during infection may inhibit CYP1A2 enzymes by as much as 90%



CYP 3A4

- Ritonavir is a **STRONG INHIBITOR**



n-desmethylozapine
(**Norclozapine**)

Clinical Case: COVID Infection & Clozapine Toxicity

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COVID-19 infection, fluctuations in the clozapine/norclozapine levels and metabolic ratio and clozapine toxicity: An illustrative case-report

K.N. Roy Chengappa^{a,*}, Jane Thomas^b, Charles E. Kahn^c, Kimberly Clinebell^d,
Kelly K. Mullen^b, Lori Arbutiski^e, Emil Ivanov^f

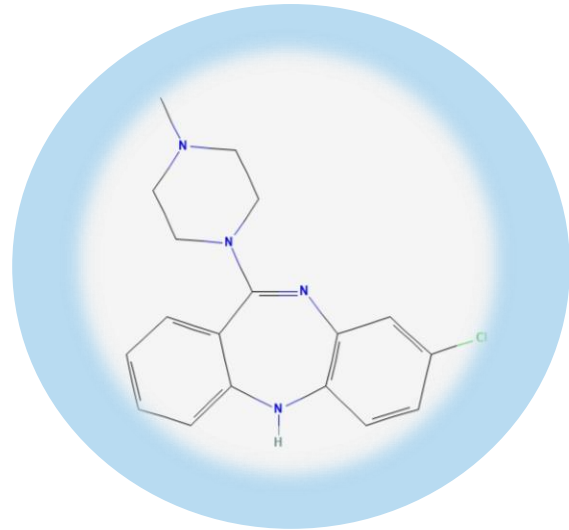


Clinical Case:

COVID Infection & Clozapine Toxicity

- 45-year-old female with treatment-resistant schizophrenia
- Started on clozapine and titrated to a dose of clozapine 350mg daily
 - Clozapine / norclozapine levels 867 / 278, not smoking
- Discharged from the hospital to a residential setting for further stabilization
- 8 days later: **COVID positive** (likely Omicron variant)
 - Symptoms – chills, fever, nasal congestion
- 2 days later: **Clozapine toxicity**
 - Symptoms – **Marked sedation, lethargic, excess salivation, required assistance to walk**
 - Clozapine / norclozapine levels 1050 / 284, smoking 8 cigarettes / day

What happened to clozapine metabolism in this case?

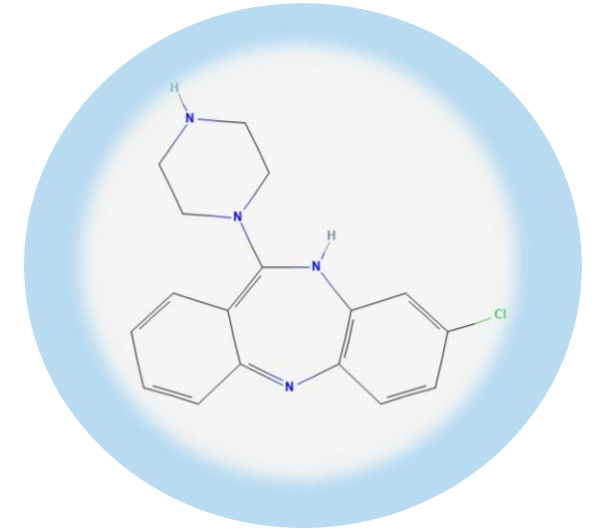


↑↑ **Clozapine
Level**

↓↓ **CYP 1A2 activity**



COVID infection caused **STRONG INHIBITION** of CYP 1A2 enzyme activity, leading to increased clozapine levels



n-desmethylozapine
(**Norclozapine**)

Clozapine Metabolism: Paxlovid

- Paxlovid is an FDA approved treatment of mild to moderate COVID infection in adults at high risk for progression to severe COVID
- Paxlovid is a combination of ritonavir and nirmatrelvir
 - Ritonavir is a **STRONG INHIBITOR** of CYP 3A4
- When Paxlovid first became available, package insert documented a **CONTRAINDICATION** for paxlovid use in conjunction with clozapine due to risk of clozapine toxicity
 - Contradiction was also listed for antipsychotics lurasidone and pimozide
- The CONTRAINDICATION for paxlovid + clozapine has since been removed from the package insert

Clozapine & Paxlovid

- The net effect of Paxlovid may not significantly impact clozapine metabolism
- Through CYP1A2 inhibition - COVID infection itself is more likely to cause clozapine toxicity
 - **IMPORTANT ASIDE:** Smoking induces CYP1A2, lowering clozapine levels
- Clozapine patients need to be monitored closely after a positive COVID test. Continued vigilance is needed if prescribed Paxlovid
 - Common signs of clozapine toxicity: Sedation (50%), delirium (20%), speech disturbance (15%), gait disturbance (13%), myoclonic jerks/seizures (18%).
- **BIG PICTURE:** Patient education is important surrounding the onset of any infection or new medication

Rapid Dissemination Initiatives

Broad dissemination to UPMC WPH Physicians & APPs, Pharmacists, Others

- Distribution of 5-slide synopsis of essential information

Development of Continuing Medical Education (CME)

- COVID19 and Clozapine Toxicity, Nirmatrelvir-Ritonavir and Psychotropic Meds

Electronic Medical Records Changes

- Examples: Implementation of drug-drug interaction warnings, creation of auto-text

National Dissemination Efforts

- SMI Advisor Tips

Initiatives to Educate & Empower Patients and Families!



Patient-Focused Education Initiative: Telephone Outreach

Marisol Piechowicz, MD

PGY4 Resident, Western Psychiatric Hospital, UPMC

Comprehensive Recovery Services Clozapine Clinic

- In 2020, CRS OP and CRS STEP physicians prescribed clozapine to 194 patients
- 183 patients were served via our collocated pharmacy within our clozapine clinic.



Patient Education: Initial Outreach

- UPMC Forbes Pharmacy provided reports of all patients prescribed clozapine
 - Patients were filtered by prescriber and clinic
 - Reports were provided to team members
- Team members agreed upon standard discussion and began phone outreach to patients at Forbes and STEP/OP
 - We attempted to reach patients and caregivers by phone first utilizing the phone numbers listed in the electronic health record (EHR)
- A letter with relevant information was mailed out to the patient's last known address listed in the EHR after two failed attempts at contact via phone
- A SmartPhrase was developed in the EHR to document conversations in encounters

Metrics

- From start date (6/1/2022) to end date (9/6/2022), we called 190 clozapine patients.
- 146 of patients called were UPMC Forbes Pharmacy and CRS/STEP OP patients. Other patients contacted included those served by LTSR and CTT.
- In total, from start of project to 9/6/2022, 146 out of 167 CRS STEP/OP patients, or 87%, had documented contact

EPIC Smartphrase

"I have counseled the patient/caregiver that Paxlovid, a recently approved drug to treat mild to moderate COVID-19 is contraindicated for patients currently receiving clozapine.

I have also counseled the patient/caregiver that COVID-19 infection can raise clozapine levels to toxicity, explained what the symptoms of toxicity may look like, and advised them to use emergency services were these symptoms to occur."

Initiative: Strengths & Challenges

Strengths

- Ability to answer follow-up questions in the moment
- Modality allowed us to reach patients and caregivers alike

Challenges

- Lack of rapport
- Confusion/miscommunication
- Difficulty reaching some individuals
- Lack of consistency
- Lack of reference material



Patient-Focused Education Initiative: Developing Written Materials

Patrick Frailey, MD

PGY4 Resident, Western Psychiatric Hospital, UPMC

Developing Written Patient Materials

- In process of telephone call initiative, we identified potential value of written material to disseminate important information to patients
- At this time there is a lack of a standardized process to develop written material for patients, specifically for individuals with schizophrenia

Accessibility

- Commonly measured with the Flesch Reading Ease Score (FRES) and its counterpart, the Flesch-Kincaid Grade Level
- Our first steps:
 - Lay out the information we thought was important for patients to know
 - Try to write it as simply as possible
 - *Measure* with the FRES and edit as necessary

Reliability

The DISCERN Instrument

- Guided our development of the brochure
 - Topics like reliable sources that are clearly disclosed, information presented objectively, and reference to opportunities for further learning
- Used as an evaluation tool by our experts

The DISCERN Instrument

Organisations are authorised to reproduce The DISCERN Instrument without permission, provided it is used in accordance with the instructions contained in this website to ensure that its methodology is uniform.

Please read the **General Instructions** before using DISCERN. Click the 'Rating this question' links for additional guidance on each question.

The DISCERN instrument and the handbook are available as a **PDF document** for good quality print copies. To view this you will need to have Acrobat Reader installed.



Once you have completed the installation, return to this page to view the **Discern PDF**.

SECTION 1

Is the publication reliable?

1. Are the aims clear?

→ RATING THIS QUESTION

No		Partially		Yes
1	2	3	4	5

HINT: Look for a clear indication at the beginning of the publication of:

- what it is about

The DISCERN Instrument - Answer Sheet

The following questions are the DISCERN instrument adapted into the Teams Form format.

Further information on DISCERN including the full instrument can be found on at www.discern.org.uk.

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Reference:

Charnock, D., Shepperd, S., Needham, G., & Gann, R. (1999). DISCERN: An instrument for judging the quality of written consumer health information on treatment choices. *Journal of Epidemiology and Community Health*, 53(2), 105–111. <https://doi.org/10.1136/jech.53.2.105>

* Required

Is the publication reliable?

1

Are the aims clear?

HINT: Look for a clear indication at the beginning of the publication of:

- what it is about
- what it is meant to cover (and what topics are meant to be excluded)
- who might find it useful

The Patient Experience

Three measurements:

- Patient knowledge measured with pre- and post-test
- Qualitative data gathered from patient focus groups
- Quantitative measurement of patient usefulness guided by the USE – Usefulness Scale for Patient Informational Material

Rate each of the statements below to show the extent to which you agree with that statement. If you completely disagree with a statement, put a cross in the circle on the far left. If you completely agree with a statement, put a cross in the circle on the far right. Use the circles in between to express your level of agreement.

If you make a mistake, draw a line through the cross and put another in the right place. Please use only one cross per statement.

This example shows how to do it: If the brochure did not help you to understand the treatment of the disease/illness at all, place your cross as shown:

The brochure	completely disagree	neutral	completely agree
...helped me to understand the treatment.	X		

Please answer each question as openly and honestly as you can to indicate the way it applies to you personally.

Please rate each of the statements below:

The brochure...	completely disagree	neutral	completely agree
1. ...contains information I need.	O		O
2. ...helped me to understand the disease/illness.	O		O
3. ...helped me to understand the treatment options.	O		O
4. ...reduced my worries about my disease/illness.	O		O
5. ...has given me courage.	O		O
6. ...has given me the hope that I will feel better again.	O		O
7. ...helps me to participate in decisions made about my treatment.	O		O
8. ...showed me how I can contribute to the success of the treatment.	O		O
9. ...encouraged me to become more active in order to improve my condition.	O		O

The brochure...

...contains information I need.

...helped me to understand the effect of COVID-19 and Paxlovid on my clozapine levels.

...helped me to understand what I should do if I get COVID-19.

...addressed my worries about the effect of COVID-19 and Paxlovid on clozapine my clozapine level.

...has given me courage that I could handle a COVID-19 infection.

...helps me to participate in decisions made about my treatment.

...showed me how I can contribute to the success of the treatment.

...encouraged me to become more active in the management of my health.

Where are we now?

The brochure has been drafted

- 6th grade reading level per FRES

Expert feedback has been solicited

- Experts were sent:
 - A copy of the brochure
 - A grading sheet for DISCERN to collect responses
 - Full information on DISCERN from the official website, including step-by-step guidance through the questions

What is COVID-19?

COVID-19 is a respiratory virus, meaning it affects the parts of your body that help you breathe.⁽¹⁾

Symptoms can be different for different people. Symptoms can be serious and even deadly, especially if you are older or have other illnesses. For some, it might feel like a mild cold, such as sniffles and sore throat, and for others they will not even notice they have it.⁽¹⁾

COVID-19 spreads easily. You can slow the spread by keeping your distance from people when possible and wearing a mask in public places. Vaccines are also available.⁽¹⁾

How do I know if I have COVID-19?

You should get tested if you have symptoms, or if you have been close to someone who has COVID-19.

Most pharmacies and drug stores carry fast tests that you can do from home.

Authors

Patrick Frailey, MD¹; Mariel Pechowicz, MD¹; Elizabeth Kistler, MD¹⁻³; Robert Cotes, MD¹; KN Roy Chengappa, MD¹⁻³, UPMC Western Psychiatric Hospital¹, University of Pittsburgh School of Medicine², and Emory University School of Medicine³.

Further Reading

For general information about COVID-19 and its treatment:

[CDC.gov/coronavirus](https://www.cdc.gov/coronavirus).

For information about serious mental illness and its treatment:

[SMIAdviser.org](https://www.smiadviser.org)

For information about Paxlovid and its use for COVID-19 infection:

www.fda.gov/media/155051/download

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CLOZAPINE

+ COVID-19



What you need to know about
COVID-19
if you take clozapine

October 2023

What does COVID-19 have to do with clozapine?

When you take a medication like clozapine, it goes into your blood. Over time, your liver removes the medication from your body.

The amount of clozapine that your doctor gives you is based on your liver working normally.

COVID-19 can change how your liver works so that it takes longer to remove the clozapine from your blood.⁽²⁾

This means that the amount of clozapine in your blood can increase and could become too high if you have COVID-19.⁽²⁾

If I get COVID-19, should I stop taking clozapine?

No! You should not stop taking clozapine even if you get COVID-19, unless your doctor tells you to do so.⁽³⁾

You should talk to both your primary care provider (PCP) **and** the doctor who prescribes your clozapine.

Do you know the warning signs of too much clozapine?

- Feeling tired, much more than usual
- Feeling confused
- Having trouble walking
- Drooling more than usual
- Muscle movements that you can't control⁽⁴⁾



What should I do if I have warning signs of too much clozapine?

- ✓ Go to the nearest emergency room.
- ✓ Try to bring a list of all your medication.
- ✓ Tell the doctor you take clozapine.
- ✓ Tell the doctor if you have COVID-19 and if you are taking Paxlovid.

What is Paxlovid?

Paxlovid is the brand name for a combination of two medicines that can treat COVID-19 by fighting the virus in your body.⁽⁵⁾

Paxlovid is used for people who have COVID-19 with mild-to-moderate symptoms and certain other factors that might increase their risk of severe illness. In these cases, Paxlovid may reduce the risk of bad outcomes, such as death or hospitalization.⁽⁵⁾

If I'm taking clozapine, can I take Paxlovid?

Maybe, but you need to be extra careful. Paxlovid might increase clozapine in your blood, just like the COVID-19 infection does.⁽³⁾

This means you need to talk to your doctors – the one that gives you clozapine **and** the one treating you for COVID-19. Usually, this is two different doctors.

Are there any other treatments for COVID-19?

Yes, there are other options.

There are other medications that work to fight the virus. Sometimes, you might not need any medication at all, or just over-the-counter medicine. Your doctor can help you decide which option is right for you.

Where are we now?

Focus groups are being recruited!

- Targeting two groups of 10 patients
- The population: patients within our UPMC Comprehensive Recovery Services (CRS) clinic with a diagnosis of schizophrenia or schizoaffective disorder who are prescribed clozapine and active in monitoring through our pharmacy.
- The session:
 - 30 minutes to take a pre-test, then review the brochure, then score it with the USE and take a post-test to measure knowledge
 - ~45 minutes of focus group discussion to collect qualitative data



Questions?

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