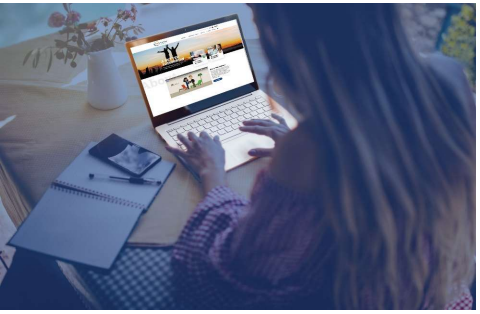
Welcome

Clozapine & LAI Virtual Forum

March 6, 2024| 4:00 – 4:45 pm ET



The Clozapine & LAI Virtual Forum is a peer-to-peer, interactive dialogue between psychiatrists, nurse practitioners, and other prescribing clinicians.

It is informal, no registration required — just join our Zoom call and share your challenges and questions on the month's trending topic around either clozapine or LAIs.

TODAY'S TOPIC:
Debating the Use of Clozapine with Fluvoxamine

Moderators

Donna Rolin, PhD, APRN, PMHCNS-BC, PMHNP-BC
Clinical Nurse Expert; Clinical Associate Professor
APA/SMI Adviser; University of Texas at Austin

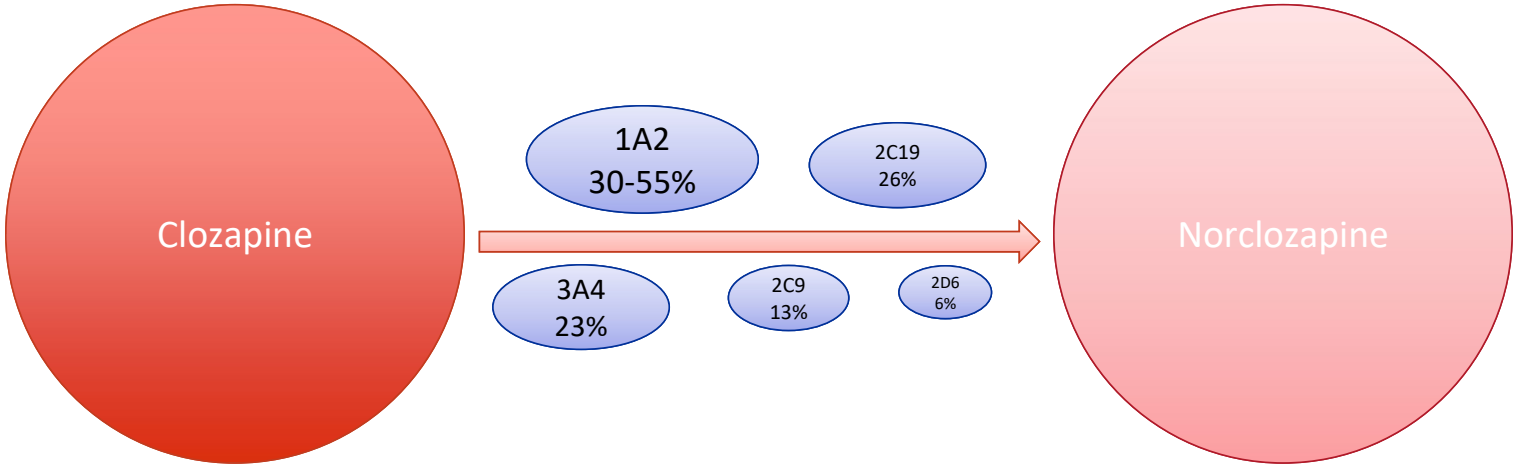
Megan Ehret, PharmD, MS, BCPP
Clinical Pharmacy Expert; Professor
APA/SMI Adviser; University of Maryland

Robert Cotes, MD
Clinical Physician Expert; Associate Professor
APA/SMI Adviser; Emory University

Discussion Questions for Virtual Forum: *Debating the Use of Clozapine with Fluvoxamine*

- Tell us about your experiences using clozapine and fluvoxamine together.
  - Why did you use this combination?
  - How did it go?
- Make your case *for* why to use clozapine and fluvoxamine together
- Make your case *against* using clozapine and fluvoxamine together

Relative Contribution of CYP Enzymes to Phase I Biotransformation

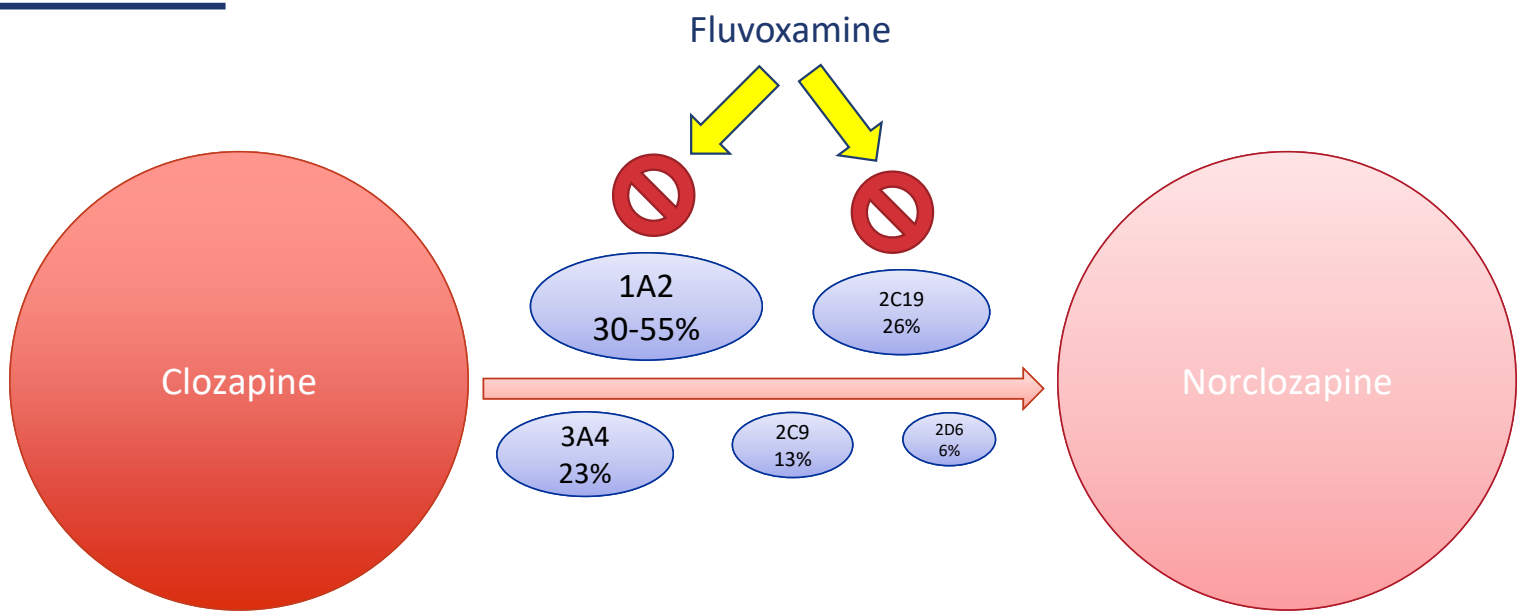


Meyer JM, Stahl SM (2019). The Clozapine Handbook: Stahl's Handbooks, Cambridge University Press.

Fluvoxamine

- FDA approval 1994
- Indication: Children, adolescents, and adults with OCD
- USPI information in the “Warnings and Precautions” section:
  - Clozapine: “Clozapine levels may be increased and produce orthostatic hypotension and seizures”
- Substrate
  - CYP1A2
  - CYP2D6
- Strong inhibitor
  - CYP1A2
  - CYP2C19
- Drug Interactions Flockhart Table, available at https://drug-interactions.medicine.iu.edu/MainTable.aspx

Fluvoxamine



- Meyer JM, Stahl SM (2019). The Clozapine Handbook: Stahl's Handbooks, Cambridge University Press.

Interpreting the MR

Expected value for nonsmokers

<1.0	1.3	>1.7	>3.0

+ Inducer (smoking, carbamazepine, omeprazole)

OR

CYP 1A2 ultra-rapid metabolizer

+ Inhibitor (Fluoxetine, paroxetine, bupropion, etc)

OR

CYP 1A2 or CYP 2D6 poor metabolizers

++ Inhibitor (ciprofloxacin, fluvoxamine)

OR

Viral or bacterial illness

Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.

Kinetic Effects from Fluvoxamine + Clozapine

- Fluvoxamine approximately doubles the elimination half-life of clozapine (Chang et. al 2004)
- Increase clozapine level (2-2.5 Lu et al., 2000, Verdoux et al., 2023) and increased concentration dose ratio
- Increased metabolic ratio (1.5x Costa-Dookhan et al., 2020)
- Data for smokers and clozapine + fluvoxamine vary, but one study found non-smokers had a similar MR to smokers + fluvoxamine (Augustin et al., 2019)
- Non-linear pharmacokinetic DDIs at higher fluvoxamine doses (Silver, 2001)

Evidence for Using Clozapine and Fluvoxamine

- Lu et al., 2018
  - 12 wk, double-blind, RCT, 85 patients randomized to clozapine 100 mg + fluvoxamine 50 mg versus clozapine 300 mg in patients of Asian ancestry
  - 12 wk levels = clozapine 663.2 ng/mL, clozapine + fluvoxamine 623.7 ng/mL;
  - MR monotherapy = 3.9; MR combined group = 6.8
  - In comparison to monotherapy, combined treatment group had attenuated weight gain, insulin resistance, fasting glucose, and decreased PANSS general psychopathology score

Manipulating the MR?

- MR >2 may imply saturation of CYP1A2 medicated metabolism (Legare et al., 2013)
- Narrative review (Costa-Dookhan et al., 2020)
  - Higher MR associated with poorer cognition (5/6 studies)
  - No association with psychopathology and the MR (6 studies)
  - Fluvoxamine increased MR and attenuated metabolic dysfunction (4 studies)

Safety Issues with Clozapine and Fluvoxamine

- Neurological symptoms associated with clozapine intoxication (Purdon and Snaterse, 1998; Peritogiannis et al., 2005)
- Extrapyramidal symptoms (Spina and de Leon, 2007)
- Effects “not completely predictable” (Spina and de Leon, 2014)
- Particular caution with poor metabolizers
- Death occurred at Beijing Anding Hospital, “combination no longer recommended” (Ruan et al., 2023)

Clinical Considerations

- Decrease total number of clozapine tablets thereby possibly increasing adherence
- Situations where maximum dose clozapine (e.g. 900 mg) is used in ultra-rapid metabolizers and plasma levels remain subtherapeutic
- Possible role in attenuating metabolic side effects (but other options are available)
- If you stop fluvoxamine, use TDM and increase the clozapine dose to prevent relapse
- **In summary, pharmacokinetic expertise, awareness of other DDIs, slow titration, careful monitoring, and TDM is essential (Verdoux et al. 2023)**

FEEDBACK

Please help us improve the Clozapine & LAI Virtual Forum by completing this survey:
http://smiadviser.org/forumfeedback

Pre-submit Cases

www.smiadviser.org/vfcases

UPCOMING VIRTUAL FORUM

4/3/24 @4:00-5:00 PM ET

VMAT2 inhibitors

For additional questions and resources – join the Clozapine and LAI Centers of Excellence Exchange Community

- www.smiadviser.org/cloz_lai_signup