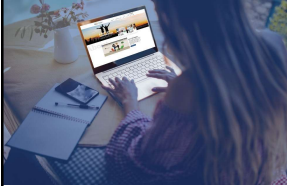


## WELCOME



# Clozapine & LAI Virtual Forum

June 2023 | 4:00 – 4:45 pm ET

The Clozapine & LAI Virtual Forum is an all-new, 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:

Non-antipsychotic, pharmacologic augmentation strategies to partial responders on clozapine

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## MODERATORS

### **Robert Cotes, MD**

SMI Adviser Physician Expert; Emory University

Dr. Robert Cotes, MD, is an Associate Professor at Emory University School of Medicine in the Department of Psychiatry and Behavioral Sciences. He has interest in clozapine, characterizing persistent symptoms of schizophrenia, understanding cardiometabolic side effects of antipsychotic medications, and first episode psychosis.

### **Donna Rolin, PhD, APRN**

SMI Adviser Nursing Expert; University of Texas, Austin

Dr. Donna Rolin is Clinical Associate Professor and the Director of the Psychiatric Mental Health Nurse Practitioner program at the University of Texas with 23 years of experience in psychiatric nursing, including inpatient, community, forensic, and older adult settings.

### **Megan Ehret, PharmD, MS, BCPP**

SMI Adviser Pharmacy Expert, University of Maryland

Dr. Megan Ehret is a Professor at University of Maryland School of Pharmacy in the Department of Practice, Sciences, and Health Outcomes Research and is Co-Director of the Mental Health Program. She is a Past-President of the American Association of Psychiatric Pharmacists. Her current interests include psychotropic medication adherence and the incorporation of the psychiatric pharmacist in practice.

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## Discussion Questions for Virtual Forum:

- Do you systematically measure clozapine response? If so, how?
- Is it worth adding non-antipsychotic pharmacologic augmentation strategies to partial responders on clozapine?
  - If so, what medications have you tried?
    - What have you had success with?
    - What has not worked?
  - Do you try to use certain medications to target different symptom domains (e.g., negative or cognitive symptoms)?

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## If you prescribe clozapine, you likely will encounter partial responders and non-responders

- 40% response rate to clozapine
  - Mean PANSS reduction 22 points (25.8% from baseline)
  - 32% in the short-term
  - 39% in the long-term
- Suggests 12% to 20% of people with SCZ are clozapine-resistant
- Minimize the delay to clozapine initiation if possible

- Siskind, D., Siskind, V., & Kisely, S. (2017). Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. *Can J Psychiatry, 62*(11), 772-777. Yoshimura B, Yada Y, So R, Takaki M, Yamada N. The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. *Psychiatry Res. 2017 Apr;250:65-70. doi: 10.1016/j.psychres.2017.01.064. Epub 2017 Jan 24. PMID: 28142068.*

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## A systematic approach helps to evaluate response

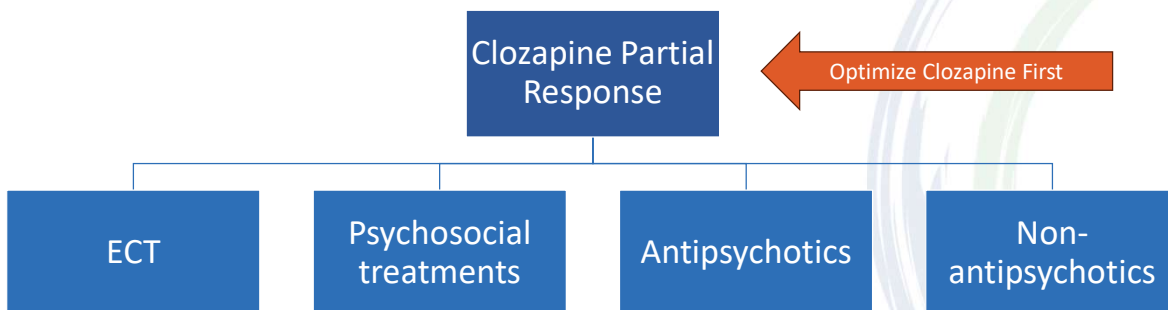
- Guess?
- CRDPSS
- PANSS-6
- PANSS
- BPRS
- Functioning
- Goals
- CGI-I/CGI-S

Score	CGI-S (Severity)	CGI-I (Improvement)
1	Normal	Very much improved
2	Borderline mentally ill, not at all ill	Much improved
3	Mildly ill	Minimally improved
4	Moderately ill	No change
5	Markedly ill	Minimally worse
6	Severely ill	Much worse
7	Among the most extremely ill patients	Very much worse

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology*. US Department of Health, Education, and Welfare, Public Health Service

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## Augmentation Options



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## TRRIP Consensus Guidelines – Clozapine Augmentation

- Recommendations which reached  $\geq 75\%$  agreement for refractory positive symptoms
  - Raise clozapine plasma levels to  $\geq 350$  ng/ml
  - Wait for a delayed response at an adequate dose (mean 15 wks, median 12 wks)
  - Combine with second antipsychotic (aripiprazole, amisulpride)
  - Augment with ECT
  - CBT
  - Psychosocial interventions

• Wagner, E., Kane, J. M., Correll, C. U., Howes, O., Siskind, D., Honer, W. G., . . . Hasan, A. (2020). Clozapine Combination and Augmentation Strategies in Patients With Schizophrenia -Recommendations From an International Expert Survey Among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. *Schizophr Bull.* doi:10.1093/schbul/sbaa060

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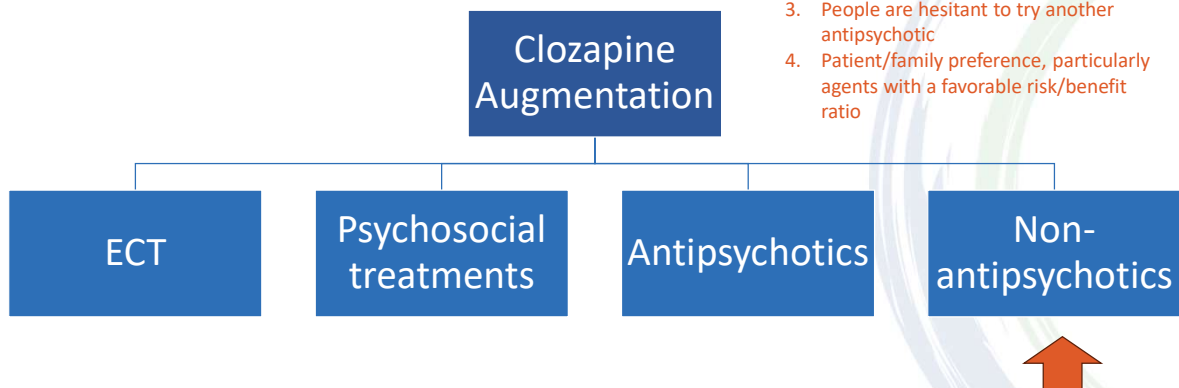
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## Augmentation Options



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## Some non-antipsychotic augmentation options – Finally!

Adapted from Meyer JM, Stahl SM. The Clozapine Handbook: Stahl's Handbooks: Cambridge University Press; 2019.  
Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry: Wiley; 2021.

Option	Notes
Famotidine	1 RCT (Meskanen et al., 11/30 on clozapine), improved positive and general sx
Gingko biloba	1 RCT (Doruk et al.) 42 patients, decreased NS (not positive nor overall)
Lamotrigine	Potential role, may reduce alcohol use, mixed evidence and two outlying studies
Memantine	2 RCTs show benefit in positive, negative, and cognitive sx
Minocycline	8 PBO-controlled studies. "Probably not effective" – Maudsley handbook
Mirtazapine	1 RCT (Zoccali et al.) benefit for negative sx
Omega-3 triglycerides	"Modest, and somewhat contested evidence" -Maudsley handbook
Pimavanserin	1 case series (Nasrallah et al., N=6) improvement in positive sx
Topiramate	5 RCT some improvement in positive sx and general psychopathology
Sodium benzoate	1 RCT (Lin et al.) improved positive and negative sx
Sodium valproate	At least 9 RCTs, small effect on general psychopathology; kinetic interaction, neutropenia

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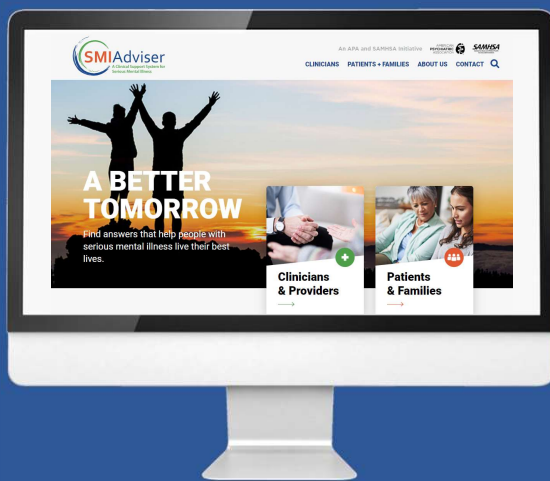


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## FEEDBACK

Please help us improve the Clozapine & LAI Virtual Forum by completing this survey:

<http://smiadviser.org/forumfeedback>



## Pre-submit Cases

[www.smiadviser.org/vfcases](http://www.smiadviser.org/vfcases)

## UPCOMING VIRTUAL FORUM

LAI Research Methodology Issues

September 6, 2023 @4-4:45pm ET

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

- [www.smiadviser.org/cloz\\_lai\\_signup](http://www.smiadviser.org/cloz_lai_signup)

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## UPCOMING WEBINAR



### Updates in Proper Use and Administration of Long-Acting Injectable Antipsychotics

August 10, 2023 | 3 – 4 PM ET

Ericka Crouse, PharmD

Review the indications, dosing, preparation, administration, monitoring and documentation of long-acting injectable antipsychotic agents. It will compare the differences between each agent in terms of frequency of dosing, need for oral overlap, administration sites, needle sizes required, and differences in storage and preparation.

[SMIadviser.org/education](https://SMIadviser.org/education)

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## Meta-analysis of augmentation strategies

- Positive symptoms
  - Aripiprazole (SMD 0.48)
  - Fluoxetine (SMD 0.73)
  - Sodium valproate (SMD 2.36)
- Negative symptoms
  - Memantine (SMD 0.56)
- Promising interventions
  - ECT
  - Minocycline
  - Gingko
  - Lithium

Siskind, D. J., Lee, M., Ravindran, A., Zhang, Q., Ma, E., Motamarri, B., & Kisely, S. (2018). Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis. *Aust N Z J Psychiatry, 52*(8), 751-767.

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## Meta-review

- 21 meta-analyses or systematic reviews included
- Recommendation grade (based on quality of meta-analysis or systematic review)
  - B: FGA, SGA, antidepressants, ECT
  - C: Mood stabilizers/anticonvulsants, rTMS
  - D: Glutamatergics, tDCS, CBT
- “the beneficial effect of adding an antidepressant or antipsychotic cannot be attributed with good evidence to a specific compound”

Wagner, E., Lohrs, L., Siskind, D., Honer, W. G., Falkai, P., & Hasan, A. (2019). Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance. *J Psychopharmacol*, 33(4), 423-435.

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## Clozapine-Resistant Schizophrenia

- TRRIP TRS criteria + failure to respond to adequate clozapine treatment
  - Trough serum levels measured on two occasions at least one week apart  $\geq 350$  ng/mL
    - If blood levels not feasible, minimum dosage 500 mg/day
  - Therapy duration  $\geq 3$  months
  - Adherence  $\geq 80\%$  of prescribed doses at the prescribed dosage

Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., . . . Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*, 174(3), 216-229.

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