**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 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.
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)?

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

A systematic approach helps to evaluate response

<table>
<thead>
<tr>
<th>Score</th>
<th>CGI-S (Severity)</th>
<th>CGI-I (Improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Very much improved</td>
</tr>
<tr>
<td>2</td>
<td>Borderline mentally ill, not at all ill</td>
<td>Much improved</td>
</tr>
<tr>
<td>3</td>
<td>Mildly ill</td>
<td>Minimally improved</td>
</tr>
<tr>
<td>4</td>
<td>Moderately ill</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>Markedly ill</td>
<td>Minimally worse</td>
</tr>
<tr>
<td>6</td>
<td>Severely ill</td>
<td>Much worse</td>
</tr>
<tr>
<td>7</td>
<td>Among the most extremely ill patients</td>
<td>Very much worse</td>
</tr>
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Augmentation Options

- ECT
- Psychosocial treatments
- Antipsychotics
- Non-antipsychotics

Optimize Clozapine First
TRRIP Consensus Guidelines – Clozapine Augmentation

- Recommendations which reached ≥75% agreement for refractory positive symptoms
  - Raise clozapine plasma levels to ≥ 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


Augmentation Options

- **Clozapine Augmentation**
  - ECT
  - Psychosocial treatments
  - Antipsychotics
  - Non-antipsychotics

- When to Consider Non-Antipsychotics
  1. You have tried the other options and still have a partial response
  2. You don’t have access ECT or evidence-based psychosocial interventions
  3. People are hesitant to try another antipsychotic
  4. Patient/family preference, particularly agents with a favorable risk/benefit ratio
Some non-antipsychotic augmentation options – Finally!


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

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
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

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

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”


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 ≥ 350 ng/mL
    • If blood levels not feasible, minimum dosage 500 mg/day
  • Therapy duration ≥ 3 months
  • Adherence ≥ 80% of prescribed doses at the prescribed dosage