WELCOME

Clozapine & LAI Virtual Forum
November 2, 2022 | 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:
Management of Clozapine Induced Constipation
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.

Susanna Every-Palmer, PhD, MSc, FRANZCP, MBChB
Associate Professor; Head of Department of Psychological Medicine, University of Otago

Dr. Every-Palmer is an academic psychiatrist who is passionate about using multidisciplinary research collaborations to inform the highest quality evidence-based care for people with mental illness. Alongside her role in the university, Susanna is concurrently employed at the Central Regional and Forensic Services.
Today’s Format

- 20 minute discussion among the group
- 15 minute presentation by Dr. Every-Palmer
Discussion Questions

• How are you currently screening clozapine-treated patients for constipation?
• Has anyone worked with a clozapine-treated patient that has had severe complications due to constipation/CIGH, such as a bowel obstruction?
• Are you using medications to help prevent slow gut/constipation, and if so what agents are you using?
• Do you use pharmacologic treatments for constipation prophylactically?
• Have you ever used one of the secretagogue medications (e.g. linaclotide or lubiprostone) for clozapine-treated patients?
Managing Clozapine Induced Gastrointestinal Hypomotility

Susanna Every-Palmer
SMI Adviser Virtual Forum
2 November 2022
CIGH: Five ‘S’s of clozapine and the GI system:

- **Slow** gut: from esophagus to rectum
- **Significant**: Gastrointestinal hypomotility is probably clozapine’s *most common* side effect
- Often **silent**: The patient may not report any symptoms (e.g. constipation)
- **Serious**: Your clozapine treated patients are much more likely to die of GI complications than agranulocytosis.
- **Speed** things up: When starting clozapine, a laxative should also be prescribed
SLOW: Spatiotemporal mapping: baseline activity
How common is CIGH: bowel motility studies

- Constipation in at least 30% (Shirazi et al, 2016)
- What about slow gut? Bowel motility study (Every-Palmer et al 2016)
- Half on clozapine, other half on other antipsychotics
- Stopped any laxatives
- Measured colonic transit times using ROMs

*Figure 5.0. Sitzmarks radiopaque markers: O-rings; D-rings; and tri-rings.*
Bowel motility studies

• For other antipsychotics the median transit time was 23 hours
• This is normal
• For the clozapine treated patients median transit time was 104 other group and normative values (p<0.0001)
• This is definitely not normal
• 80% of clozapine treated patients had colonic hypomotility

Every-Palmer, Nowitz, Huthwaite et al. EBioMedicine, 2016

Fig. 3. Colonic transit time (in hours) for non-clozapine and clozapine-treated participants.
“Smartpill” studies

• Only 18% of people had normal studies
• 82% had dysmotility in at least one region of the gastrointestinal tract
• 59% multi-regional dysmotility.
• 41% delayed gastric emptying
• 71% delayed small bowel transit
• 50% delayed colon transit in 50%.
SERIOUS

• Untreated bowel obstruction/ pseudo-obstruction leading to distension, necrosis, perforation or sepsis.
• Obstruction leading to inhalation of faeculent vomitus
• Faecal stasis leading to infection
Life threatening CIGH

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>73%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>55%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>55%</td>
</tr>
<tr>
<td>Constipation</td>
<td>45%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
</tr>
<tr>
<td>Septic shock (tachycardia, hypotension)</td>
<td>32%</td>
</tr>
</tbody>
</table>

Red flag symptoms: moderate to severe abdominal pain and abdominal distension.
Pharmacoepidemiology

For every thousand patients treated with clozapine:

- 800 will have objective slow gut
- At least four will develop serious gastrointestinal complications, from which one will die.
"...First, we examined the reliability of asking about constipation compared with asking about Rome constipation criteria in inpatients treated with clozapine (n = 69). Second, we examined the diagnostic accuracy of (1) self-reported constipation and (2) the Rome criteria, compared with the reference standard of gastrointestinal motility studies."
Relying on self-reported constipation

- Only about ¼ self-reported constipation but ¾ had CIGH on bowel motility testing.
- “Inquiring about constipation had a sensitivity of 18% for diagnosing CIGH—a grim performance for a diagnostic test, worse even than a toss of a coin.”
SPEED THINGS UP: Pharmacological treatment for antipsychotic related constipation

Which laxative is best?

“DUNNO”

What about the newer agents?
PORIRUA PROTOCOL for all clozapine treated patients
Guidance to prevent clozapine-related constipation

1. Start regular docusate & senna 2 tabs noce
2. Be alert for RED FLAGS which might suggest serious pathology
3. Monitor bowel function regularly
Be aware patients under-report constipation symptoms
For monitoring consider using Bristol Stool Chart

<table>
<thead>
<tr>
<th>If still constipated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RED FLAGS</strong></td>
</tr>
<tr>
<td>Urgent medical review required for the following:</td>
</tr>
<tr>
<td>- Moderate to severe abdominal pain lasting over an hour OR</td>
</tr>
<tr>
<td>- Any abdominal pain/discomfort lasting over an hour AND one or more of the following: abdominal distension, diarrhoea (rao bloody), vomiting, absent or high pitched bowel sounds, metabolic acidosis, haemodynamic instability, leukocytosis, or other signs of sepsis.</td>
</tr>
</tbody>
</table>

2. Review within 48 hours
Increase docusate & senna by one tab every 2 days until no longer constipated or max of 2 tabs bd reached

<table>
<thead>
<tr>
<th>If still constipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>If bowel function satisfactory</td>
</tr>
<tr>
<td>Continue treatment and monitoring</td>
</tr>
</tbody>
</table>

3. Rectal examination to exclude impaction
   a) If impacted stop docusate and senna
      Discuss with expert (may need enemas, manual disimpaction)
   b) If not impacted continue docusate & senna 2 tabs bd

<table>
<thead>
<tr>
<th>If still constipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>If diarrhoea develops</td>
</tr>
<tr>
<td>Gradually reverse steps until bowel function satisfactory. First reduce then stop any macrogol. Then reduce docusate &amp; senna by one tab every 2 days</td>
</tr>
</tbody>
</table>

4. Review within 48 hours
Add macrogol 1 sachet bd

<table>
<thead>
<tr>
<th>If still constipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue treatment and monitoring</td>
</tr>
</tbody>
</table>

5. Review within 48 hours
Discuss with expert for formulation of individualised regime (may include increased dose of macrogol and enemas)
Does the Porirua Protocol work?

- Significant reduction of 48 hours transit time (p<0.009).
- Severe hypomotility dropped from 64% to 21%
- No change in self-reported constipation or ROME III constipation symptoms

<table>
<thead>
<tr>
<th>Before Porirua Protocol</th>
<th>After Porirua Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2 cases of serious CIGH per 100 person years (95% CI 5.1—12.6)</td>
<td>1.1 cases of serious CIGH per 100 person years (95% CI: 0.2–3.1)</td>
</tr>
</tbody>
</table>

RR = 0.13 (0.40–0.04)
Back to the key points

- Carefully monitor serum levels if infection of change of smoking
- The 5 “S”s of CIGH
- Particularly **SILENT** - self-reported constipation has low sensitivity in predicting hypomotility.
- **SPEED THINGS UP**: prophylactic laxatives for all clozapine treated patients. Not PRN

EMAIL: Susanna.every-palmer@otago.ac.nz
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
The Practice of Pharmacists Administering LAIs
December 7 @ 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