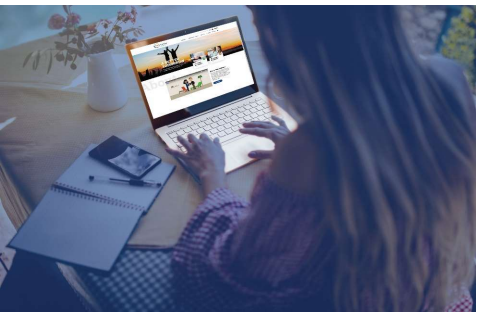
WELCOME

# 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.

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## 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

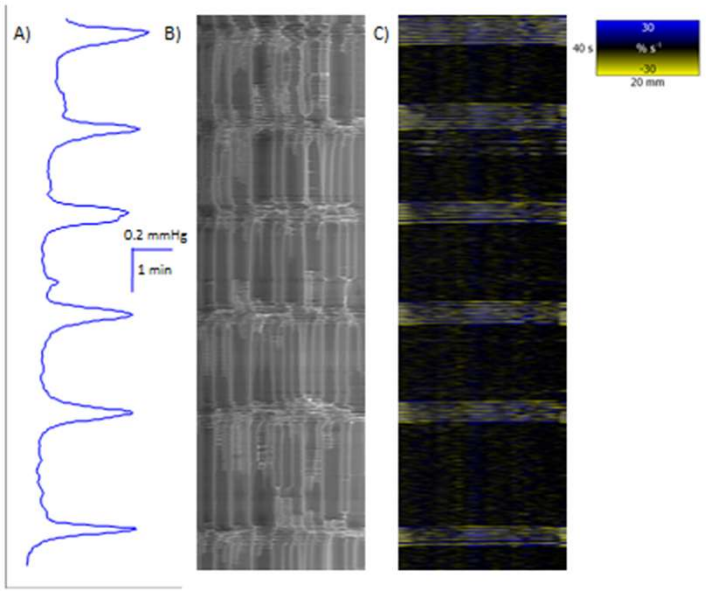
Susanna Every-Palmer
SMI Adviser Virtual Forum
2 November 2022

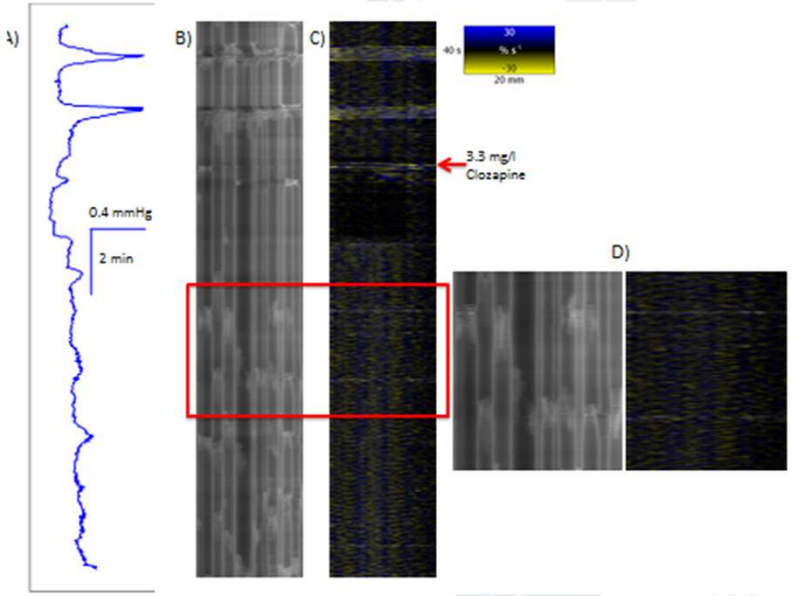
An APA and SAMHSA Initiative

# 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: 0-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

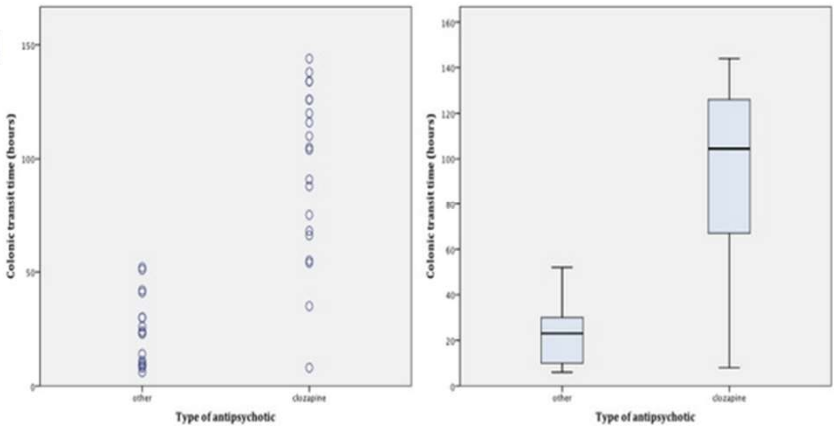
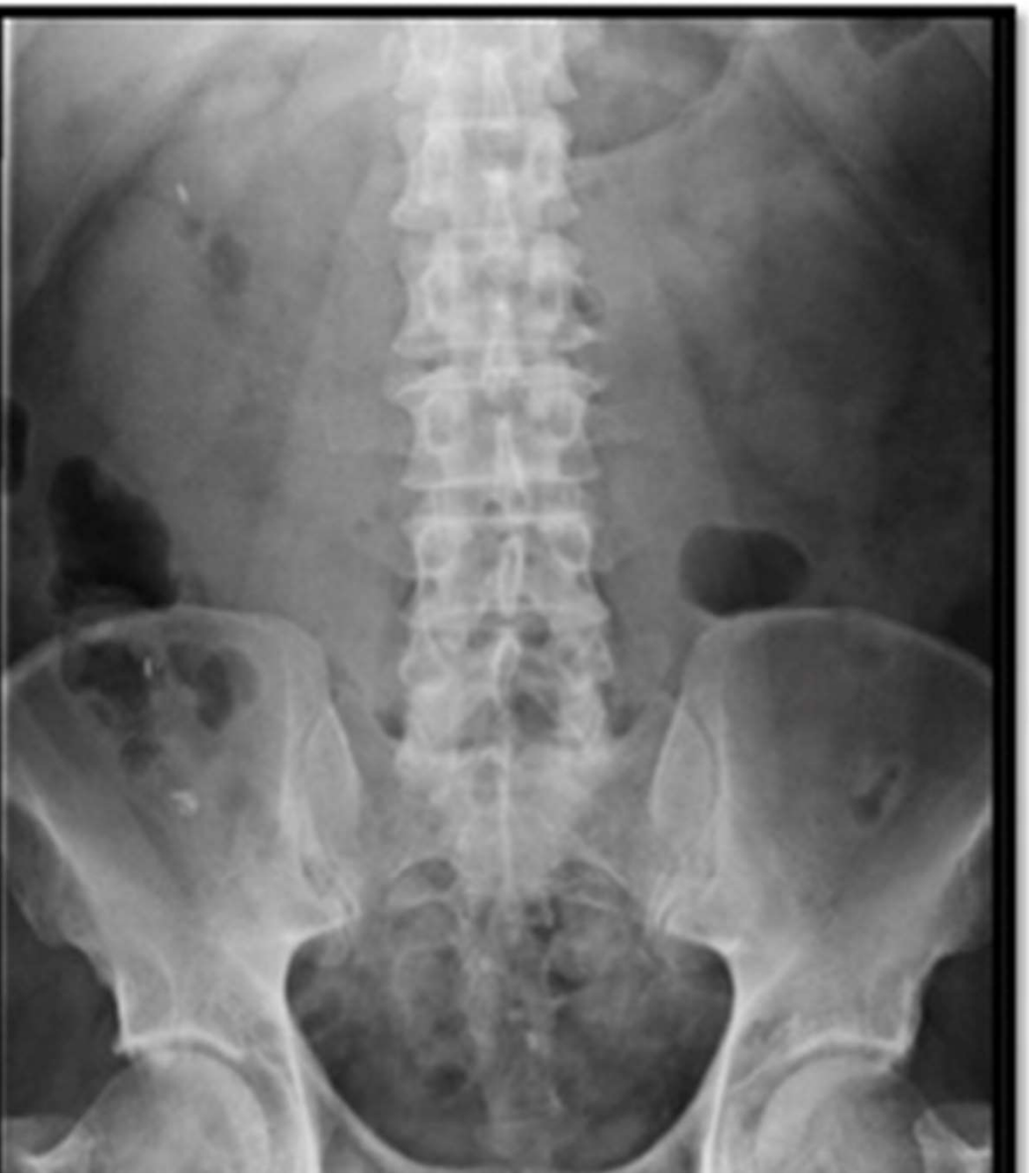
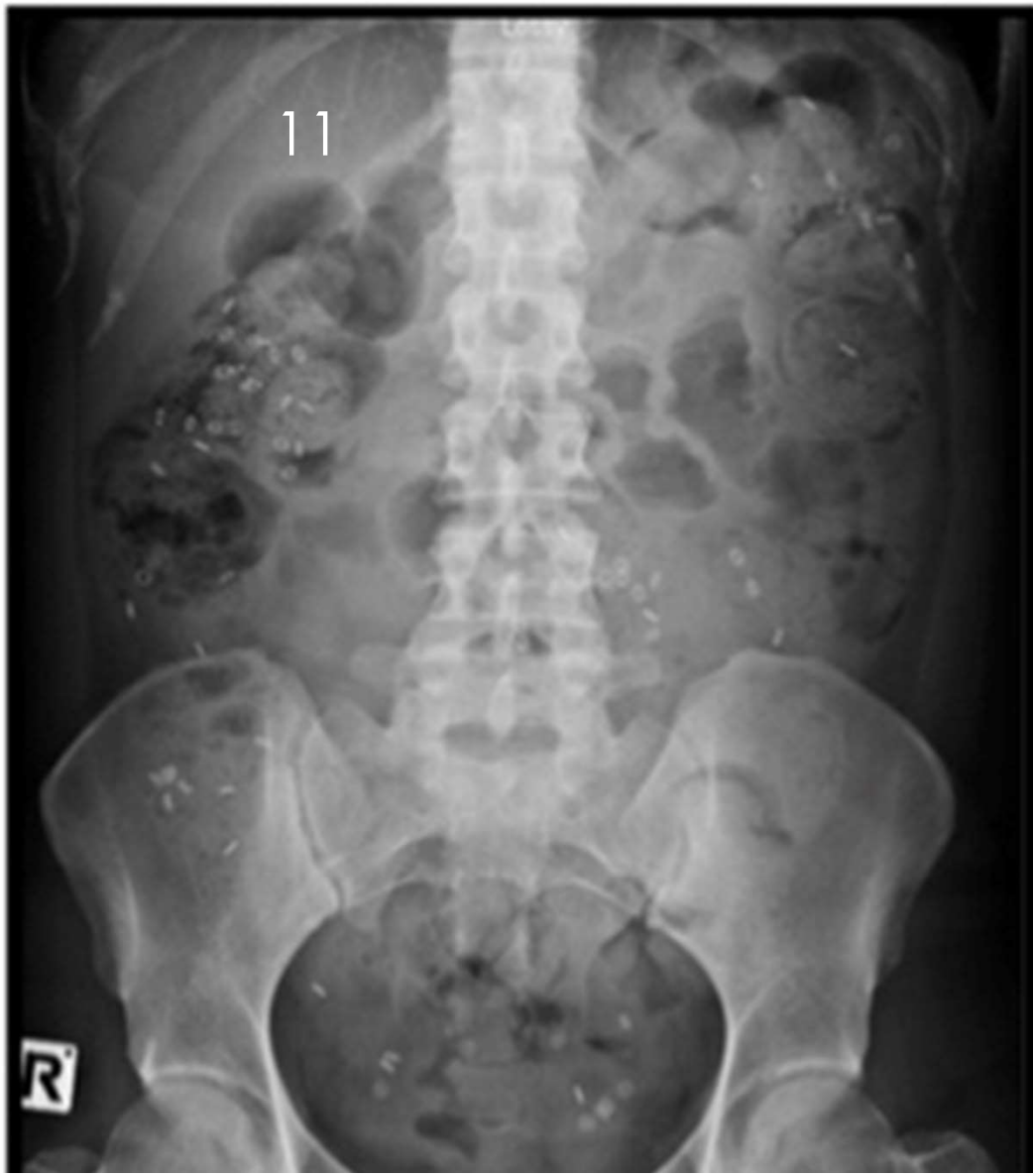



Fig. 3.
Colonic transit time (in hours) for non-clozapine and clozapine-treated participants.

# “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%.

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# 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

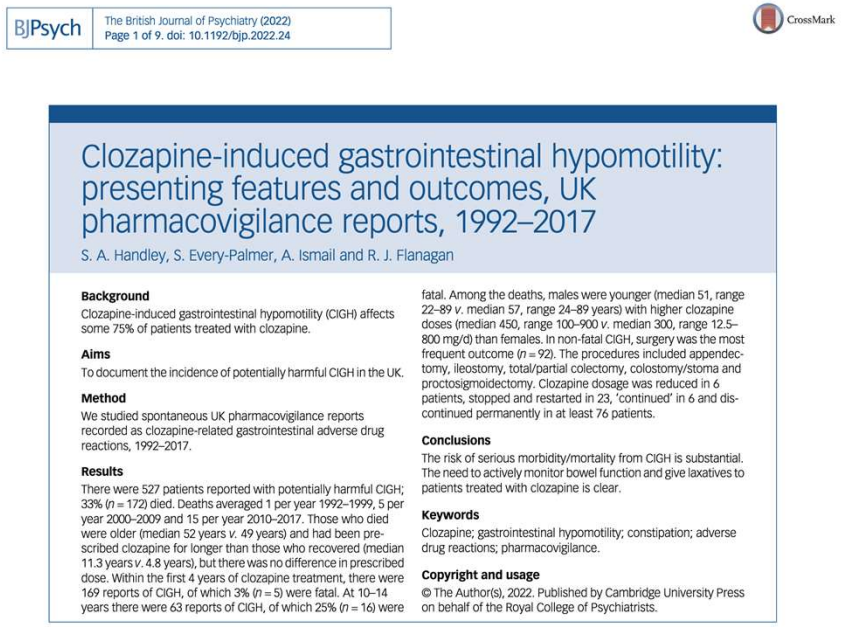
| Clinical finding | Frequency |
|---|---|
| Abdominal pain | 73% |
| Abdominal distension | 55% |
| Vomiting | 55% |
| Constipation | 45% |
| Diarrhoea | 32% |
| Nausea | 23% |
| Septic shock (tachycardia, hypotension) | 32% |

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.



BJPsych The British Journal of Psychiatry (2022)
Page 1 of 9. doi: 10.1192/bjp.2022.24

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## Clozapine-induced gastrointestinal hypomotility: presenting features and outcomes, UK pharmacovigilance reports, 1992–2017

S. A. Handley, S. Every-Palmer, A. Ismail and R. J. Flanagan

**Background**
Clozapine-induced gastrointestinal hypomotility (CIGH) affects some 75% of patients treated with clozapine.

**Aims**
To document the incidence of potentially harmful CIGH in the UK.

**Method**
We studied spontaneous UK pharmacovigilance reports recorded as clozapine-related gastrointestinal adverse drug reactions, 1992–2017.

**Results**
There were 527 patients reported with potentially harmful CIGH; 33% ($n = 172$) died. Deaths averaged 1 per year 1992–1999, 5 per year 2000–2009 and 15 per year 2010–2017. Those who died were older (median 52 years *v.* 49 years) and had been prescribed clozapine for longer than those who recovered (median 11.3 years *v.* 4.8 years), but there was no difference in prescribed dose. Within the first 4 years of clozapine treatment, there were 169 reports of CIGH, of which 3% ($n = 5$) were fatal. At 10–14 years there were 63 reports of CIGH, of which 25% ($n = 16$) were fatal. Among the deaths, males were younger (median 51, range 22–89 *v.* median 57, range 24–89 years) with higher clozapine doses (median 450, range 100–900 *v.* median 300, range 12.5–800 mg/d) than females. In non-fatal CIGH, surgery was the most frequent outcome ($n = 92$). The procedures included appendectomy, ileostomy, total/partial colectomy, colostomy/stoma and proctosigmoidectomy. Clozapine dosage was reduced in 6 patients, stopped and restarted in 23, 'continued' in 6 and discontinued permanently in at least 76 patients.

**Conclusions**
The risk of serious morbidity/mortality from CIGH is substantial. The need to actively monitor bowel function and give laxatives to patients treated with clozapine is clear.

**Keywords**
Clozapine; gastrointestinal hypomotility; constipation; adverse drug reactions; pharmacovigilance.

# SILENT: Diagnosing CIGH

ELSEVIER

Schizophrenia Research
Volume 220, June 2020, Pages 179-186

## Constipation screening in people taking clozapine: A diagnostic accuracy study

Susanna Every-Palmer FRANZCP, PhD [a], Stephen J. Inns FRACP, MD [b], Pete M. Ellis FRANZCP, PhD [a]

"…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?


Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological treatment for antipsychotic-related constipation (Review)

Every-Palmer S, Newton-Howes G, Clarke MJ

Every-Palmer S, Newton-Howes G, Clarke MJ.
Pharmacological treatment for antipsychotic-related constipation.
*Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD011128.
DOI: 10.1002/14651858.CD011128.pub2.

www.cochranelibrary.com

Pharmacological treatment for antipsychotic-related constipation (Review)
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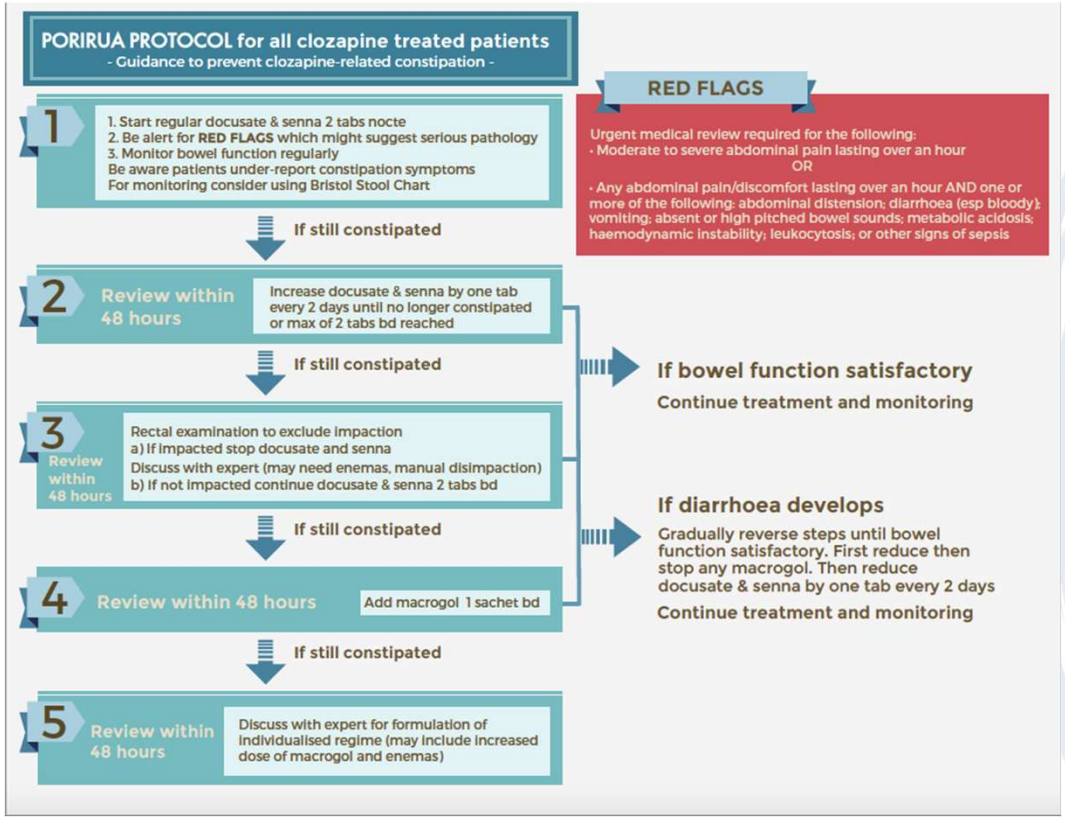
WILEY



# 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

| Before Porirua Protocol | After Porirua Protocol |
|---|---|
| 8.2 cases of serious CIGH per 100 person years (95% CI 5.1-–12.6) | 1.1 cases of serious CIGH per 100 person years (95% CI: 0.2–3.1) |

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