Clozapine Induced Constipation

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Learning Aims

- Understand the mechanism of physiological (non iatrogenic) constipation & the underlying risk factors
- Understand the pharmacological basis of clozapine induced constipation
- Have knowledge of the prevalence of clozapine induced constipation
- Have knowledge of the presenting symptoms
- Have knowledge of the remedial measures available

Therapeutic Employment of Clozapine

* Licensed indications:

Clozapine is the only effective evidence-based treatment for TRS

Psychosis in Parkinson's disease (BNF)

* Unlicensed indication:

Intramuscular clozapine is an unlicensed product made in the Netherlands by Brocacef and imported to the UK.

Why constipation occurs? (Physiological)

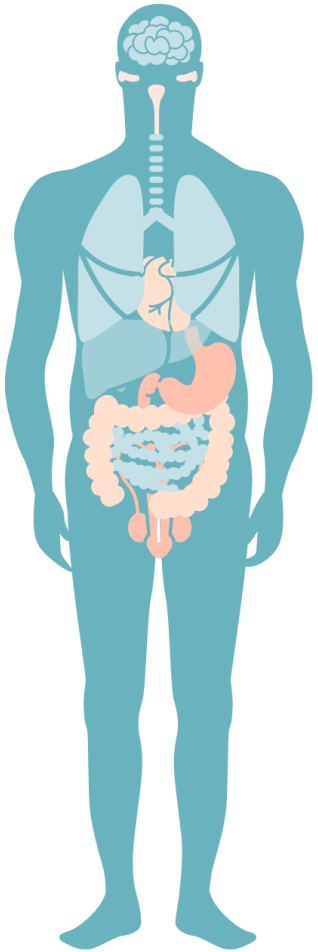
- Clozapine interacts with a range of muscarinic, serotonergic and other receptors to have marked effects on the GI tract.(1)
- Moderate serotonin 5HT3 antagonism
- High affinity for histamine H1 receptors

Risk Factors for Constipation

Neurological

Fluid

Low fiber diets



Hypomotility

Age and Sex

Sedentary lifestyle

Pharmacological Mechanism

* Clozapine receptor profile :

Antagonistic actions at:

dopamine (D1, D2, D3, D4, D5)

serotonin (5-HT1A, 5-HT2A, 5-HT2C),

muscarinic (M1, M2, M3, M5),

α1- and α2-adrenergic,

and histamine (H1) receptors

Agonist at muscarinic (M4) receptors

Pharmacological Mechanism

* Proposed pharmacological mechanisms:

- Gastrointestinal motility is reduced via peripheral muscarinic anticholinergic activity.
- Serotonergic antagonism reduces intestinal nociception (4)
- Histamine H 1 receptor antagonism which leads to sedation.
- Norclozapine increases risk for constipation through potent agonist activity at δ opioid receptors (4)

Prevalence of Clozapine Induced Constipation

- Constipation can occur in up to 60% of patients.
- Gastric outlet obstruction can occur in up to 33% of patients.
- Ileus is seen in close to 1.3% of patients.
- There have been case reports on fatal bowel ischemia on patients treated with clozapine.
- Mortality from complications secondary to constipation is higher with clozapine than other antipsychotic medications.
- The prevalence and severity of constipation may be dose dependent (2).

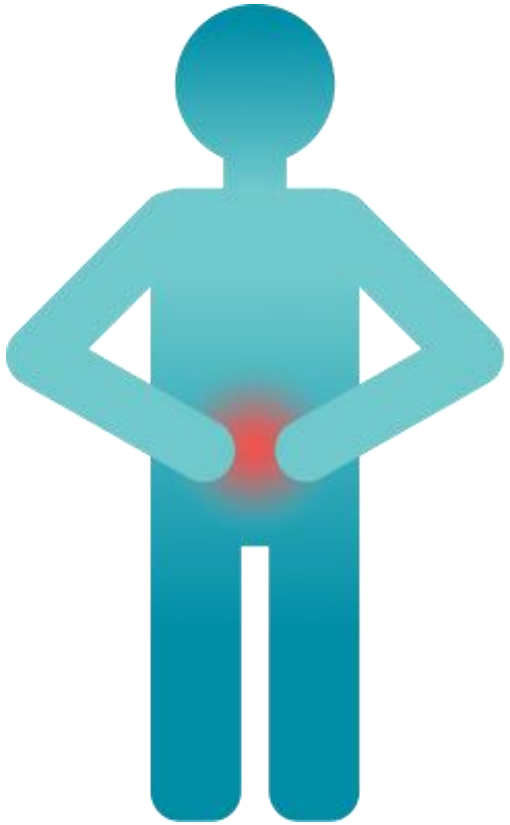
Prevalence of Clozapine Induced Constipation

- Constipation is difficult, incomplete, or infrequent evacuation of dry, hardened faeces.
- It is an often disregarded with a prevalence rate of 25%.
- Patients typically have risk factors for constipation, including sedentary lifestyle, obesity, reduced fiber intake, and dehydration (4)
- Future research must address possible preventative measures, both lifestyle and pharmacotherapeutic interventions (4).

Clinical Presentation

* Physical presentation:

- Abdominal bloatin
- Pain on defecation
- Rectal bleeding
- Spurious diarrohea
- Low back pain



Clinical Presentation

The following also suggest that the patient may have difficult rectal evacuation:

- Feeling of incomplete evacuation
- Digital extraction
- Tenesmus
- Enema retention

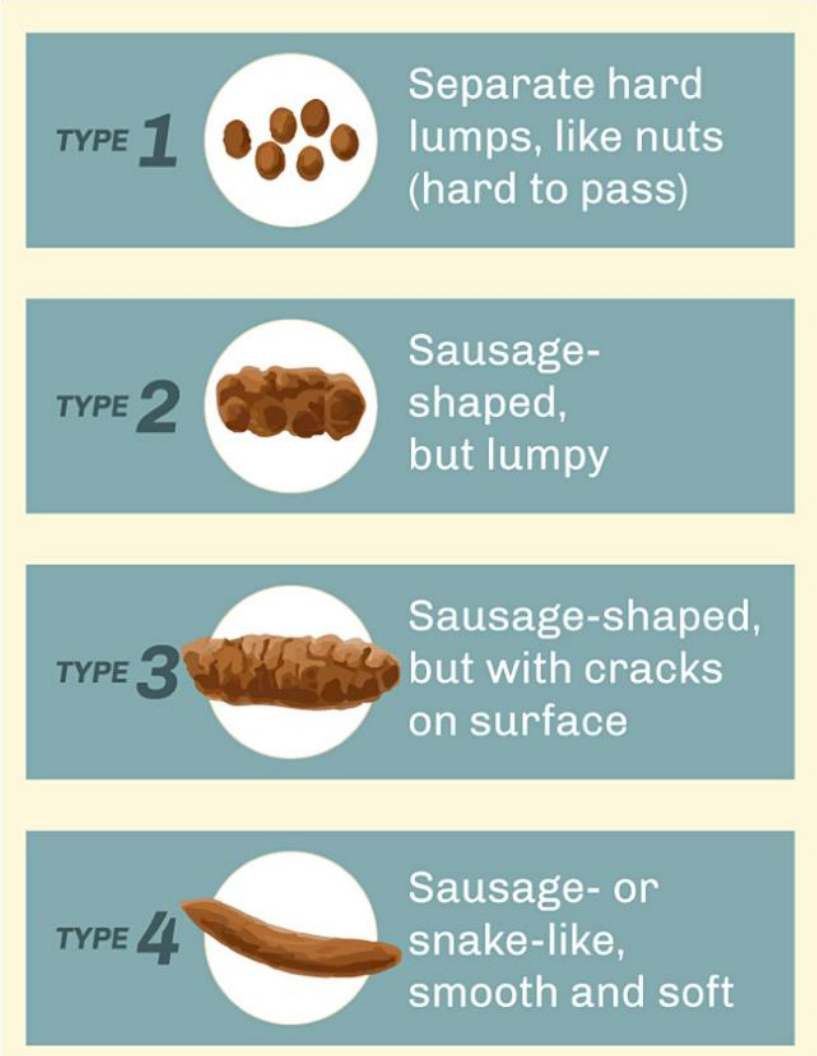
Clinical Presentation

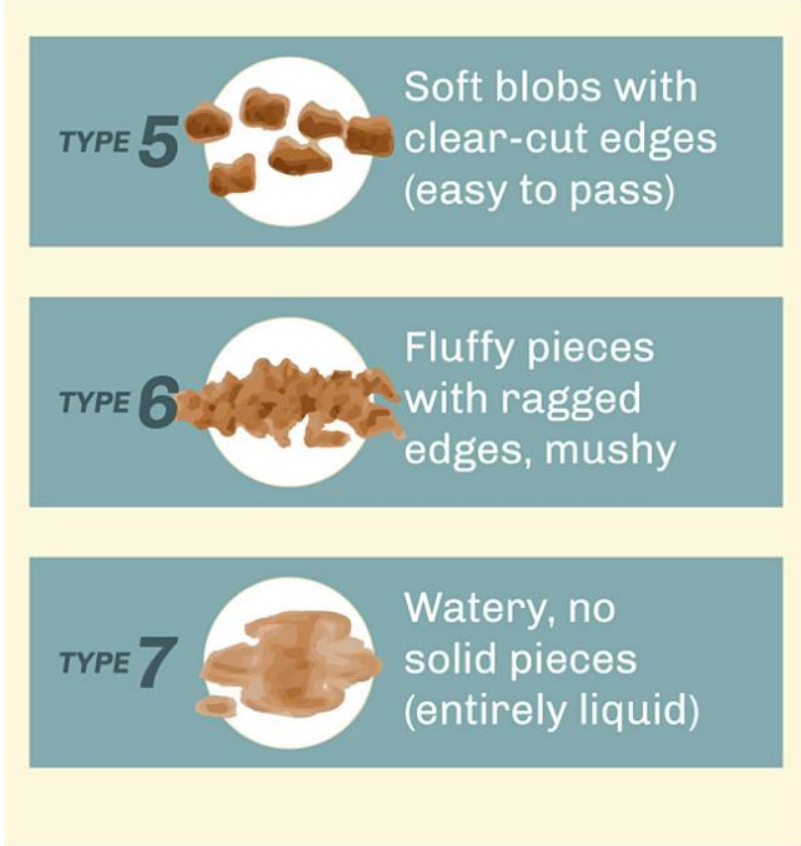
The following signs and symptoms, if present, are grounds for particular concern:

- Rectal bleeding
- Abdominal pain
- Inability to pass flatus
- Vomiting
- Unexplained weight loss

Clinical Presentation

- Levels:





NICE
1.Self management advice

a) Eating a healthy, balanced diet and having regular meals.
b) Drinking an adequate fluid intake, especially if there is a risk of dehydration.
c) Increasing activity and exercise levels.
d) Helpful toileting routines

Acute Interventions

a) Manage any underlying cause of constipation.

b) Advise on lifestyle measures, such as increasing dietary fibre, fluid intake, and activity levels.

c) If these measures are ineffective, or symptoms do not respond adequately, offer treatment with oral laxatives using a stepped approach:

Acute Interventions

- Offer a bulk-forming laxative first-line, such as ispaghula.
- If stools remain hard or difficult to pass: add or switch to an osmotic laxative, such as a macrogol.
- If stools are soft but difficult to pass, or there is a sensation of inadequate emptying: add a stimulant laxative.

Acute Interventions

a) If the person has opioid-induced constipation:

- Do not prescribe bulk-forming laxatives.
- Offer an osmotic laxative and a stimulant laxative (or docusate).

b) Advise to gradually reduce and stop laxatives

Management of chronic constipation

a) For the initial management:

- Manage any underlying secondary cause.
- Advise on lifestyle measures.
- Manage any faecal loading and/or impaction first, if present.

Management of chronic constipation

b) If the person has ongoing symptoms- offer drug treatment with oral laxatives using a stepped approach.

- Offer initial treatment with a bulk-forming laxative such as ispaghula.
- If stools remain hard or difficult to pass: add or switch to an osmotic laxative, such as a macrogol.
- If stools are soft but difficult to pass or there is a sensation of inadequate emptying: add a stimulant laxative.

Management of chronic constipation

c) Consider the use of prucalopride or lubiprostone:

- If at least two laxatives from different classes have been tried at the highest tolerated recommended doses
- For at least 6 months
- The prokinetic prucalopride stimulates gastrointestinal motility.
- The secretory drug lubiprostone acts locally to increase intestinal fluid secretion and improve colon transit.

Management of chronic constipation

d) If the person has opioid-induced constipation:

- Do not prescribe bulk-forming laxatives.
- Offer an osmotic laxative and a stimulant laxative.

Management of chronic constipation

e) Gradually titrate the laxative dose(s) up or down aiming to produce soft, formed stool without straining at least three times per week.

Prophylactic Strategies-Laxatives

* Porirua protocol:

- Two tablets of docusate sodium with sennoside B
- If no bowel movement for two days – increase dose of docusate sodium with sennoside B by one tablet.
- If still constipated, increase the dose again by one tablet.
- If remains constipated, a rectal examination should be performed to exclude impaction.
- If constipation persists, add one macrogol sachet BD.
- If constipation is ongoing refers to gastroenterologist.

Prophylactic Strategies-Laxatives

* Lubiprostone:

- Lubiprostone is a prostaglandin
- Increase in chloride rich luminal secretions
- No significant contraindications
- Adverse effects: nausea, diarrhoea and headache.

Prophylactic Strategies

- Reviewing medication regimen…
- Non pharmacological

Red Flags for constipation in patients on Clozapine

* Moderate to severe abdominal pain which lasts for more than one hour
* Any abdominal pain or discomfort which lasts for more than one hour and one or more of:
  - Abdominal distension
  - Vomiting
  - Haemodynamic instability
  - Metabolic acidosis
  - Diarrhoea, especially if bloody
  - Absent or high-pitched bowel sounds
  - An elevated white blood cell count
  - Additional signs of sepsis

Monitoring

- Baseline:

Clinicians as part of routine clinical practice should actively ask about symptoms of constipation, including the frequency and difficulty of defecation.

- Ongoing:

Protocols for monitoring constipation in clozapine-treated patients should be implemented when clozapine initiation takes place. This may utilize the Bristol stool chart, a widely used system to monitor stool frequency and consistency.

Case Study

- A45-year-old male patient with a 27-year history of treatment-resistant residual schizophrenia (with much institutional care) and excellent past physical health (he had no prior history of constipation or other gastrointestinal symptoms or diseases) had been treated with clozapine (400 mg/die) for the past 5 months before his admission in our hospital, obtaining a significant psychopathological benefit. At the time of hospitalization, he resided in a community mental health facility and was also receiving lorazepam (2.5 mg/die) for a recurrent starting insomnia and sertraline (100 mg/die) as augmentation for his antipsychotic (negative symptoms) medication.His plasma clozapine levels were within therapeutic limits (490 ng/mL for clozapine and 280 ng/mL for norclozapine) (6)

Case Study

- On admission, the patient reported a three-week history of severe constipation and subjective abdominal distention (without pain), followed by two episodes of biliary vomiting on the same day (6)
- In the week before his hospitalization, he also complained of intermittent fever (temperature > 38° C) and coughing fits (6)
- Physical examination revealed diffuse abdominal tenderness which was soon accompanied by marked abdominal distention (without pain)), colon cord sensation in the right iliac fossa and decreased bowel sounds. (6)

Case Study

- Creatinine, urea and electrolytes, in fact, were normal and liver function values were within the normal range.
- A contrast enema also revealed no gross structural lesions.
- Based on those findings, a diagnosis of intestinal occlusion was made.
- Over the following week, the ileus resolved with conservative treatment (intravenous fluids, fleet enema and rectal washout), while clozapine therapy had been decreased.

Case Study

- After the intestinal obstruction had resolved, the patient fully recovered within four days of treatment, had regular bowel motions within a week and preventive measures (high-fiber diet, adequate fluid intake, stool softeners and exercise) were used to ensure that clozapine therapy could be safely continued (6)

Any Questions?

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