# Medication Safety Series: MSS27

## Clozapine-induced Gastrointestinal Hypomotility (CIGH)


**Summary**

- Patients and staff need to have awareness that Clozapine may **impair motility of the entire gastrointestinal system**. On a few occasions, cases have been **fatal**.
- Patients should **seek medical attention immediately** (before next dose is taken) if constipation occurs.
- Clozapine is **contraindicated** in patients with paralytic ileus.
- Particular **care** should be taken when prescribing clozapine for the following patients:
  - receiving other medications with **anticholinergic properties** - such as some antipsychotics, antidepressants, procyclidine and drugs used to manage clozapine-induced hypersalivation – or which otherwise **cause constipation**, such as opioid analgesics
  - history of **colonic disease** or a history of lower abdominal surgery
  - aged **60 years** and older
  - **obese**, **poor diet** (low fibre intake) or **low levels of exercise**
  - **poor bowel habit**

  Consider a **prophylactic laxative** as appropriate.

- At **each clinical contact** patients should be **asked about their bowels**- utilising tools such as the **Bristol Stool Chart** as appropriate.
- Any patient with **type 1 or 2 stools** and/or RED FLAGS* should be **referred** to a medical or physical health practitioner for further investigation and treatment.
  **bowels not opened for 48 hours, crampy abdominal pain lasting >1 hour, distension, nausea or vomiting, not passing wind, painful bloating, diarrhoea (especially if bloody)*
- **Treatment** is dependent upon the individual circumstance, including a **review of other medication**, consideration as to the **clozapine dose** and **laxative use**.


**Background**

- **Clozapine may impair motility of the entire gastrointestinal system** from the oesophagus to the rectum, mainly due to its anticholinergic properties but antagonism of serotonergic and histamine H1 receptors may contribute, and concomitant medications may exacerbate the problem
- The manifestation of this effect ranges from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus. **On a few occasions, cases have been fatal.** Oesophageal reflux and indigestion symptoms can also occur.
- Warnings are provided in the Summary of Product Characteristics (SPC) and Patient Information Leaflet and in the BNF. However, in August 2017, a Coroner investigating a death raised concerns that healthcare professionals might have a lack of awareness about the risks of serious adverse effects and their fast onset. This led to awareness-raising in the Drug Safety Update, October 2017
- **Clozapine-related constipation may reduce the patient's quality of life and lead to discontinuation of clozapine with subsequent deterioration in mental health**

**Prevalence**

- Hypomotility has been reported in up to 75% of patients receiving clozapine. The SPC for Clozaril® lists constipation as a very common (>1/10) adverse reaction, with a reported incidence in the literature of up to 60%. Intestinal obstruction, paralytic ileus and faecal impaction are listed in the SPC as very rare (<1/10,000)
- In the UK, up to March 2022, there were 1,025 Yellow Card reports of constipation (5 fatal) associated with clozapine. There have also been 507 reports of gastrointestinal obstruction (41 fatal) and 191 reports of faecaloma (8 fatal).
- A systematic review and meta-analysis of 32 studies [Shirazi et al (2016)], identified that patients on clozapine are significantly more likely to be constipated than those on other antipsychotics
- It often occurs early in treatment, can persist throughout treatment and may be dose/plasma-level related although it has been reported in doses as low as 50 mg daily.

**Recognising & minimising risk**

- Clozapine is **contraindicated** in patients with paralytic ileus
- The **risk** of CIGH **must not be underestimated**. **Prior** to initiation, patients and their carers should be **warned about the risk** and advised to **seek medical attention immediately** (before next dose is taken) if constipation occurs. Provide and go through the C&M patient information leaflet.
- Although there is evidence that patients are at risk of CIGH regardless of age, sex, dose and duration, **particular care** should be taken when prescribing clozapine for the following patients:
  - receiving other medications with **anticholinergic properties** - such as some antipsychotics, antidepressants, procyclidine and drugs used to manage clozapine-induced hypersalivation – or which otherwise **cause constipation**, such as opioid analgesics
  - history of **colonic disease** or a history of lower abdominal surgery
  - aged **60 years** and older
  - **obese**, **poor diet** (low fibre intake) or **low levels of exercise**
  - poor bowel habit
- For high-risk patients, consider prescribing prophylactic laxatives at the same time as initiating clozapine
- It has also been suggested that fever, infection, or inflammation may inhibit the metabolism of clozapine leading to increased plasma levels and risk of constipation. Stopping smoking, with no dose adjustment, may also increase the risk.

**Monitoring**

- At each clinical contact, **all** patients on clozapine should:
  - be asked about their bowel function, utilising the Bristol stool chart as necessary and appropriate to identify possible constipation. The Bristol Stool Chart should be used at least 3 monthly to ensure bowel function can be ascertained.
  - be offered advice about preventative measures such as an increase in dietary fibre, maintaining adequate fluids (especially if hypersalivation is a problem) and increasing activity levels.
- Any patient with type 1 or 2 stools and/or RED FLAGS* should be referred to a medical or physical health practitioner for further investigation and treatment
  **bowels not opened for 48 hours, crampy abdominal pain lasting >1 hour, distension, nausea or vomiting, not passing wind, painful bloating, diarrhoea (especially if bloody)*

**Treatment of constipation**

- If constipation occurs during treatment with clozapine, it is vital that it is actively treated; if left untreated it can progress to intestinal obstruction, faecal impaction or bowel perforation.

- Accurate assessment of constipation is essential to determine the extent of the problem, other factors which may be exacerbating the situation and to exclude any complications.
- Consider stopping any other medication with anticholinergic and/or constipating effects
- If onset is during initiation, consider slowing down the up-titration
- Although worth considering, clozapine dose reduction may not be successful. In cases of severe, life-threatening constipation, consideration should be given to stopping treatment with clozapine.
- When necessary, seek advice from a clinical pharmacist, medic or gastroenterologist. Patients who have an acute onset of symptoms, have severe symptoms, or who are unresponsive to treatment must be referred to a specialist for further investigation.

**Laxative treatment**

- There are no specific guidelines on the treatment of clozapine-related constipation and insufficient data to support which laxatives are the safest and most effective. In cases of slowed gastrointestinal transit time fibre is unlikely to be helpful. **Bulk-forming laxatives**, such as Fybogel®, are likely to make the problem worse and **should not be used** (but may have a role to play in prevention as a source of fibre)
  - **First line options:**
    - Stimulant laxative – preferred option: Senna, 15 mg at night
      - Takes 12 hrs for therapeutic effect
      - **NB can be given to inpatients as symptomatic relief (pre-printed on chart)**
    - Osmotic laxative – preferred option: Macrogols, 1 sachet daily
      - Must be given regularly, takes several days for therapeutic effect
      - Need to ensure good fluid intake for therapeutic effect
      - Better tolerated than Lactulose (Cochrane review)
      - Monitor sodium, potassium and magnesium levels with long-term use
  - **Second-line options**
    - Stool softener – preferred option: Docusate sodium, 100 mg twice daily
      - Takes 1-2 days for therapeutic effect
      - Has mixed stimulant / softener effect
    - Suppositories – preferred option: Glycerol suppositories, 1 to be inserted when required
      - **NB can be given to inpatients as symptomatic relief (pre-printed on chart)**
    - Enema – preferred option: Sodium citrate micro enema, 1 to be used when required

| Laxative | Time to Effect | Key Point(s) |
|---|---|---|
| ***Osmotic laxatives*** | | |
| Lactulose | 2 – 3 days | • Adequate fluid intake recommended.<br>• Can cause bloating and/or colic if given in large dose. |
| Macrogols<br>(e.g. Molaxole, Laxido, Cosmocol or Movicol) | 2 – 3 days | • Requires intake of a large volume of water<br>• Licensed for use in faecal impaction |
| ***Surface-wetting laxatives*** | | |
| Docusate sodium | 12 – 72 hours | • Weak evidence of efficacy<br>• Probably acts as both a softening agent and a stimulant.<br>• May be useful for patients who find it difficult to consume an adequate amount of fluid. |
| ***Stimulant laxatives*** | | |
| Senna | 8 – 12 hours | • Short-term use only |
| Bisacodyl | 6 – 12 hours | • Short-term use only |
| ***Rectal laxatives*** | | |
| Glycerol suppositories | 15 – 30 minutes | • Lubricating and weak stimulant.<br>• Can be used for hard or soft stools |
| Bisacodyl suppositories | 15 – 180 minutes | • Avoid if hard stools as have no softening effect. |
| Sodium Citrate Enema | 5 – 15 minutes | • Useful to remove hard, impacted stools.<br>• Correct administration important to prevent damage to rectal mucosa.<br>• Licensed for occasional use only.<br>• Use with caution in the elderly or people at risk of sodium and water retention. |
| Phosphate Enema | 2 – 5 minutes | • Used to remove hard, impacted stools.<br>• Correct administration important to prevent damage to rectal mucosa.<br>• Licensed for occasional use only.<br>• Contraindicated in people who have signs of dehydration or significant renal impairment. |
| Arachis Oil Enema | Retention enema – used overnight and warmed before use. | • Useful for hard, impacted stools. Should not be used<br>• Licensed for occasional use only.<br>• **Do not use in patients with a peanut allergy.** |
| ***Bulk forming laxative*** | | |
| Ispaghula husk<br>(e.g. Fybogel) | 2 – 3 days | • **Not recommended for treatment of clozapine-induced constipation**<br>• May have a role as a fibre supplement in the prevention of constipation but must be stopped if constipation occurs<br>• Adequate fluid intake is important to reduce the risk of intestinal obstruction. |