Zaponex Fact Sheet
Constipation

Important Information

The information provided in this fact sheet is intended for healthcare professionals and should not be used as a patient information leaflet.

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

Background

SmPC statement
The Summary of Product Characteristics for Zaponex (clozapine) states that constipation is a very common (>1/10) side effect of Zaponex.[1] "Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia (see section 4.8). On rare occasions, these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medication known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and anti-parkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery, as these may exacerbate the situation. It is vital that constipation is recognised and actively treated."[1]

Paralytic ileus is a contraindication for clozapine use.[1]

Constipation
Following the Rome Criteria IV for functional constipation and opioid-induced constipation,[2] clozapine-induced constipation can be diagnosed when 2 or more of the following symptoms arise or worsen when initiating, changing, or increasing clozapine therapy:

a) Straining during at least 25% of defaecations
b) Lumpy or hard stools (Bristol Stool Form Scale 1-2) more than 25% of defaecations
c) Sensation of incomplete evacuation more than 25% of defaecations
d) Sensation of anorectal obstruction/blockage more than 25% of defaecations
e) Manual manoeuvres to facilitate at least 25% of defaecations (*e.g.*, digital evacuation, support of the pelvic floor)
f) Fewer than 3 spontaneous bowel movements per week

In addition, loose stools are rarely present without the use of laxatives.

Clozapine-induced constipation
Constipation is a recognised side effect of clozapine; the reported incidence varies between 9.4 and 80%.[3–8] Meta-analysis established a pooled prevalence of clozapine-associated constipation of 31.2%.[9] Higher rates were found in studies that had clozapine-associated constipation as primary outcome measure as compared to those that did not specify this as an outcome measure,[9] suggesting that this side effect may be under-reported when patients are not actively questioned. Similar to non-clozapine-treated populations,[2] some studies suggested that constipation may affect females more often than males, possibly due to higher clozapine plasma levels.[8,10] The risk of

developing constipation but also its severity is greater with clozapine than with other antipsychotics.[7,9,11] The risk of subsequent ileus or fatal ileus is also substantially higher;[9,11,12] world-wide adverse drug reaction data relating to clozapine-induced gastrointestinal hypomotility (CIGH) from the Uppsala Monitoring Centre demonstrated a particularly strong association between clozapine and the terms megacolon, paralytic ileus, and intestinal obstruction.[10]

Table 1 shows the risk factors for clozapine-induced constipation. Clozapine dose and plasma levels seem correlated to the risk[8,12,13] and severity of constipation,[7,14] although not all studies could confirm this association.[9,15] Importantly, using a low dose certainly does not eliminate the risk.[10] Factors that interact with clozapine metabolism, such as caffeine intake, infection, or certain co-medication, can lead to increased plasma levels and, therefore, could also increase the risk of developing constipation.[16] Additional risk factors for constipation include older age, the first four months of clozapine treatment and a history of bowel surgery, constipation or gastrointestinal pathology.[16–18] However, comorbidities such as hypothyroidism, diabetes mellitus, Parkinson's disease and multiple sclerosis are also known to predispose to constipation. A meta-analysis showed that the rate of constipation is considerably higher in inpatient settings (40.5%) than in outpatient (26.2%) and mixed (22.2%) settings.[9] Risk factors that are typically exacerbated in inpatients include dehydration, infection, smoking cessation, change in diet, concurrent medication and immobility.[19]

Table 1. Risk factors for clozapine-induced constipation.[19]

Female sex	Increasing age (esp. elderly)
Obesity	Poor diet
Inactivity/immobility	Dehydration
Poor bowel habit	No laxative use
Hospital inpatient stay	History of constipation
Recent initiation of clozapine (highest risk in first 4 months)	Concomitant medication known to cause constipation (Table 2)
High clozapine dose / plasma levels (e.g. during infection or after stopping smoking)	Comorbidities associated with increased constipation risk (e.g. Parkinson's disease, diabetes mellitus, hypothyroidism, MS)
History of bowel surgery	History of gastrointestinal pathology

Another important risk factor for the development of constipation is the use of concomitant drugs that can also induce constipation (Table 2). In particular, drugs that also have anticholinergic propensities, such as certain drugs to combat hypersalivation and extrapyramidal symptoms, should be avoided in clozapine-treated patients. In a recent study, only 11% of patients with reported CIGH were recorded as receiving other potentially constipating medications.[10]

Table 2. Medication associated with constipation.[20]

Group	Examples
Analgesics	Non-steroidal anti-inflammatory agents, opiates, tramadol
Anticholinergics	Hyoscine hydrobromide, pirenzepine, atropine, biperiden[8]
Psychotropic agents	Antidepressants (e.g. TCAs),[12,21] antipsychotics, antiparkinsonian drugs
Anticonvulsants	Phenytoin
Antihistamines	Loratadine, cetirizine, fexofenadine
Antihypertensives	Calcium channel antagonists, clonidine, hydralazine, methyldopa
Bisphosphonates	Pamidronate, risedronate
Chemotherapeutic agents	Vinca derivatives
Diuretics	Furosemide, hydrochlorothiazide
Metal ions	Aluminium (antacids, sucralfate), barium sulphate, bismuth, calcium, iron, heavy metals (arsenic, lead, mercury)
Resins	Cholestyramine, polystyrene

Although constipation is a common side effect of clozapine use, clinicians are often unaware of their patients' irregularities. One reason for this could be that psychiatric health care professionals may often not systematically assess gastrointestinal problems[9] or have insufficient medical expertise. Awareness of CIGH is generally poor; only 50% of psychiatric nurses are aware that clozapine can cause constipation, baseline monitoring of long-stay patients hardly involves assessment of bowel function and also general surgical staff are usually not informed about this side effect. Most importantly, clozapine treatment guidelines rarely mention the CIGH spectrum, let alone advise on its management.[10,22] It may also be difficult to properly monitor and provide care to certain groups of patients, such as those under detention or when treated as an outpatient.[23] In addition, patients may be reluctant to talk about their bowel habits, they may not be aware of these problems themselves – possibly due to reduced pain sensitivity[24,25] – and/or their recollection of bowel movements is insufficient due to the underlying psychosis and impaired memory.[23]
It is, however, very important to take constipation seriously, as the frequency is high and neglected constipation can have detrimental consequences.[9]

Serious motility impairment of the gastrointestinal system
If left untreated, CIGH can lead to serious complications such as paralytic ileus and faecal impaction, acute colonic (pseudo-)obstruction and colonic dilation, ischaemia, necrosis, colitis, perforation, bacterial overgrowth resulting in sepsis and faeculent vomit, dehydration, electrolyte imbalance, acidosis and ultimately, death.[23] Because of the possibility of these serious complications, the U.S. Food and Drug Administration (FDA) strengthened an existing warning in 2020 that untreated constipation caused by clozapine can lead to serious bowel complications.[26]
The prevalence of intestinal obstruction, ileus or faecal impaction is estimated at 0.3-0.8%.[10,12,16] The risk of clozapine-induced paralytic ileus seems to be dose-related.[12,14] Warning signs for serious motility impairment include abdominal pain, abdominal dilation, vomiting, overflow diarrhoea, absent or high-pitched bowel sounds, and signs of sepsis.[16,27,28]

Warning signs:[27,28]

Abdominal pain
Abdominal dilation
Vomiting
Overflow diarrhoea
Absent or high-pitched bowel sounds
Signs of sepsis

Palmer et al.[16] reviewed 102 cases of serious clozapine-induced motility impairment; 50% of cases appeared during the first year of treatment and the period with the greatest risk was during the first 4 months (36% of cases). The pre-onset treatment duration ranged from 3 days to 15 years. Of the 102 reported cases, 28 patients died and among these patients, clozapine doses were higher.[16] Furthermore, a study examining UK pharmacovigilance reports between 1992 and 2017 found that potentially harmful CIGH was reported for 527 patients, of which 33% died.[29] Patients who died were older and had been prescribed clozapine for longer than those who recovered, although there was no difference in prescribed dose.[29]

Strikingly, although the incidence of CIGH/ileus seems comparable to that of agranulocytosis (i.e., 0.4-0.8%), the case-fatality rate of 15-27.5% was observed to be much higher than the 2.2-4.2% of agranulocytosis; the mortality rate of ileus was 43.7%.[10,30,31] However, the observed difference in mortality rates might be (partially) explained by differences in reporting rates: due to the requirement of regular blood monitoring in the UK, it seems plausible that cases of mild neutropenia/agranulocytosis are reported (significantly) more often than cases of mild CIGH/constipation, for which no monitoring system is in place. As a result, the mortality rate of 43.7% for ileus may be an overestimation.
A retrospective cohort study in Iceland revealed an occurrence of ileus in 4 out of 188 (2.1%) clozapine-treated patients, with a mean time-to-onset of 13.7 years (minimum 8.7 years). Although none of these 4 cases were fatal, 2 required ileostomy and permanent stoma.[8] Of note, 3 out of 4 patients with ileus were also taking the anticholinergic drug biperiden.[8]

Other CIGH-related serious complications
Schizophrenia has also been associated with a high risk of appendiceal rupture in patients with acute appendicitis, with an adjusted odds ratio of 4.8 (95% CI: 1.62 – 14.19).[32] Altered pain perception and high pain thresholds in schizophrenia patients may result in delayed emergency surgery for appendicitis, resulting in perforation. In a forensic-psychiatric hospital in Germany, perforated appendicitis was observed in 6 schizophrenia patients treated with clozapine in a 14-year period.[33] The mean duration of clozapine treatment at the time of appendicitis was 26 months (range: 6 – 46 months). Three of the patients received laxatives due to chronic constipation. Furthermore, in two of the patients, subileus was found during the diagnostic procedures. While clozapine serum levels determined in the 4 weeks prior to onset of appendicitis were below 750 µg/L in all cases, the values exceeded 750 µg/L in 3 patients and 1200 µg/L in 2 patients during the course of appendicitis. Although clozapine dosages exceeded 500 mg/day only for one patient, multiple other factors could have resulted in high serum levels, including inflammation itself, smoking cessation or use of antibiotics. Three of the patients were treated with fluoroquinolone antibiotics, which can

considerably increase clozapine serum levels through inhibition of CYP1A2. All six patients recovered eventually.[33]

Other serious complications that have been reported as a result of clozapine-induced constipation include abdominal compartment syndrome (ACS) and volvulus.[34–37] ACS refers to organ dysfunction caused by an increase in intra-abdominal pressure of at least 20 mm Hg, which can impair global and regional perfusion and respiratory function, resulting in life-threatening organ dysfunction. One case report on ACS describes a 64-year old female taking clozapine who was found to have severe metabolic acidosis and anaemia, a massively dilated, stool-filled colon with a compressed inferior vena cava and decreased perfusion.[34] Her two-year history of chronic constipation was likely due to her medication regimen of clozapine, risperidone and the anticholinergic medications glycopyrrolate and benztropine. During surgical laparotomy, her ischaemic colon explosively decompressed, and the patient eventually died of severe reperfusion injury.
Furthermore, there have been case reports on clozapine-induced volvulus.[35–37] A 24-year old male on clozapine was found to have caecal volvulus with malrotation of gut and oedematous bowel.[36] Following de-rotation of caecal volvulus and right hemicolectomy, the patient did well in the postoperative period. Although caecal volvulus is associated with intestinal malrotation, CIGH could have increased the risk of caecal volvulus in this patient who already had intestinal malrotation as a predisposing factor.[36] Another patient on clozapine, a middle-aged man, developed three episodes of volvulus in the span of one year, but all were rapidly resolved by pumping air through a gastrostomy tube.[37]

Mechanism
By using radiopaque colonic markers, two studies showed that colonic transit time in clozapine patients is much longer than in the normal population.[38,39] Interestingly, it was also longer than in patients treated with other antipsychotics, suggesting that clozapine has distinct gastrointestinal effects that cannot be attributed to the specific patient group, or the use of antipsychotics in general.[38,39] According to one cross-sectional study, the median colonic transit time in clozapine-treated patients was 104.5 hours (95% CI: 73.3 – 134.7 h), which was 4.5 times longer than the reported transit time of 23 hours (95% CI: 9.6 – 36.4 h) in patients treated with other antipsychotics.[38] In addition, colonic transit times were positively correlated with clozapine plasma levels.[38]

Using novel radial and longitudinal spatiotemporal mapping techniques combined with monitoring of ambient lumen pressure in ex vivo preparations of rabbit colon (morphologically and physiologically similar to that of human colon[40]), Every-Palmer *et al*. identified the contractile patterns of mass peristalsis, fast phasic, and ripple contractions and directly qualified the effects of clozapine and norclozapine at various concentrations (within an order of magnitude of plasma levels reported in patients receiving therapeutic doses of clozapine) on contractile patterns.[14] They found that clozapine had an immediate and significant effect on gastrointestinal motility. Neurogenic contractions, i.e., the coordinated busts of longitudinal and circular contractions that occur during mass peristalsis, were impaired. At lower but therapeutically relevant clozapine concentrations, these contractions could be restored by the addition of the cholinergic agonist carbachol and to some extent by serotonin. In contrast, the opioid antagonist naxolone failed to normalise the colonic contractions that were decreased by the lowest clozapine dose,[14] undermining the hypothesis that opioid-like effects may contribute to clozapine-induced gastrointestinal hypomotility.[41] Myogenic contractions in circular muscle were impaired at the higher tested clozapine concentrations.[14] Furthermore, the results showed that norclozapine promotes rather than interferes with colonic motility,[14] unlike previous speculations that this metabolite might contribute to clozapine's

hypomotility effects.[42] Every-Palmer et al. consider it likely that norclozapine's M1 agonistic properties,[43] a molecular property not shared with any other antipsychotic,[44] account for the difference in norclozapine and clozapine's effects on colonic motility.[14] However, the stimulating effect of norclozapine was only observed at a single, high concentration, and not at lower concentrations, and the addition of clozapine to norclozapine abolished these effects.[14] Regardless, since one study showed that outpatients using laxatives had on average almost 30% higher norclozapine levels than those not using laxatives[42], this suggests that perhaps the clozapine:norclazapine ratio may be influential.

Together, these results suggest that the colonic effects of clozapine are mediated by cholinergic and serotonergic receptors, presumably via M1-M3[9,16,45] and 5HT-3[46] and 5HT-7 receptors,[47] respectively.[14] The findings of the spatiotemporal mapping study by Every-Palmer *et al.*[14] add further detail to the established theories that anticholinergic activity disrupts the normal functioning of the intestines, deranging duodenal motility, contractions, colon transit, gastrocolic reflex and postprandial increase of the colon activity.[25] That clozapine actually affects the entire gastrointestinal region was also shown in a study using wireless motility capsules. Of 17 clozapine-treated patients without known gastrointestinal dysfunction, only 18% were really without gut dysmotility; 59% of patients experienced multi-regional dysmotility, 41% had delayed gastric emptying, 71% had delayed small bowel transit and 50% had delayed colon transit.[48]

Additional support for the hypothesis that clozapine's antiserotonergic effects may also be involved in addition to the longstanding notion of its anticholinergic properties[16,46,49] was found in an observational study by Chougule et al.: the odds ratio (OR) for developing constipation during clozapine treatment compared to other antipsychotic treatment was 4.5 (95% CI 1.9-10.8), even though the anticholinergic burden of drug treatment was similar between the two groups.[7] Clozapine's antiserotonergic actions may also result in reduced intestinal nociception, which may contribute to a reduced awareness of constipation by patients.[16] While 5-HT2 (serotonin) receptor antagonism has been associated with an increased visceral pain threshold in rodents, 5-HT3 receptor antagonism was found to increase colon compliance and decrease intestinal sensitivity.[50,51] As clozapine antagonizes both 5-HT2 and 5-HT3 receptors, clozapine use may result in reduced intestinal nociception, contributing to a disparity between physical symptoms and severity of illness.[3]

Furthermore, the use of clozapine may increase the risk of constipation through its propensity to induce sedation, which may lead to lower physical activity and a more sedentary lifestyle.[9,25] A diet low in fibre and limited fluid intake, which may be more frequent in patients suffering from mental illnesses, may also add to developing constipation.[25,52]

The progression of CIGH to life-threatening conditions is associated with four main mechanisms, namely distension, ischaemia, infection and aspiration, all of which involve the accumulation of faeces within the bowel.[29] Distension, the most commonly observed mechanism and often preceding the others, is usually caused by faecal impaction, which leads to increased intraluminal pressure proximal to the impaction site. The induced distension may eventually result in perforation, especially if the diameter of the bowel exceeds 12 cm. Increased intraluminal pressure may also lead to reduced local arterial circulation and ischaemia, potentially resulting in local inflammatory reactions and necrosis, which in turn can lead to ulcers and a risk of perforation. Furthermore, distension of the bowel due to CIGH and faecal stasis may increase susceptibility to infection by certain microbial pathogens, such as *Clostridium perfringens*. Gastrointestinal stasis can promote the proliferation of intestinal flora, causing bacterial migration across the bowel wall resulting in sepsis. Lastly, gastrointestinal mass peristalses acting against an impacted mass may cause retrograde

movement of faecal matter through the pylorus into the stomach and initiate faeculent vomiting. Aspiration of this material can cause a chemical pneumonitis, pneumonia or even asphyxiation.[29]

Management

Prevention
A gastrointestinal history and/or abdominal examination is recommended in all patients prior to starting clozapine.[53] If there is pre-existing constipation, it should be adequately treated before clozapine initiation.[16] Active paralytic ileus is a contraindication for clozapine use, though a medical history of paralytic ileus is not.[1]

It is important that patients, as well as carers, clinical and nursing staff, are aware of the gastrointestinal side effects of antipsychotic treatment. It is recommended to discuss the risk of constipation and the need to prevent it before starting clozapine treatment and to provide the patient with appropriate lifestyle advice as a preventive measure. Such advice may include:

- Dietary advice (up to 25 g fibre/day); fruit and vegetable intake.[9,16,20,27,53,54]
- Fluid intake (up to 1.5 to 2 litres/day)[9,16,20,27,53,54]
- Regular exercise and mobility[9,53,54]
- Scheduling routine bathroom time after the morning or evening meal[2]
- Privacy of toileting[2]
- Elevating the feet with a foot stool or using a toilet that is lower to the ground[2]
- Do not ignore the urge to defaecate

As general advice, it is prudent to treat patients at the lowest effective clozapine dose, as this reduces the risks of most side effects. The prevalence of constipation and the consequences of serious constipation, such as paralytic ileus and obstruction, are considered to be related to dose/plasma levels,[12,13] so low doses may avoid the risks.[28]

Any concomitant medication that can also cause constipation, such as opiates and anticholinergics (Table 2), should be stopped if feasible. If this is not possible, the patient should be monitored with increased intensity and/or prophylactic laxatives may be considered. Also, for patients with a history of (clozapine-induced) constipation, or predisposition due to comorbid disorders such as hypothyroidism, diabetes mellitus, Parkinson's disease and multiple sclerosis, increased monitoring and/or prophylactic laxatives may be considered. The significance of a distended abdomen ('clozapine belly') must be recognised. Importantly, a low threshold for referral to an emergency department is warranted, as there are cases in which death occurred only hours after the first symptoms were reported and the patient had no previous symptoms of constipation.[18]

Monitoring bowel habits
Since neglected constipation can lead to severe complications, it is vital that the symptoms are recognised and the condition is actively treated at an early stage. As mentioned before, patients may not always be aware of constipation,[38] or are less likely to spontaneously report abdominal complaints. Therefore, clinicians should actively and systematically screen and monitor for symptoms and complications of constipation.[9,25,27,55–57] This monitoring may vary from questioning the patient for bowel movements to abdominal and rectal examination, depending on the patients' medical history and mental status. Weekly screening is especially advised during the first 4 months of

treatment as this seems to be a higher-risk period.[16,27,55] However, paralytic ileus can occur at any time in treatment,[12] so ongoing monitoring, at least with the frequency of blood monitoring, would be advisable.

It has been frequently reported that subjective reporting of gastrointestinal symptoms by patients on clozapine is not an accurate indicator of constipation.[16,25,38] Every-Palmer et al. examined the diagnostic accuracy of asking about constipation and the Rome constipation criteria in inpatients taking clozapine.[58] Unfortunately, the diagnostic accuracy of constipation screening was so poor that the study was terminated prematurely. The sensitivity for diagnosing CIGH was especially low in case of self-reporting constipation (18%), as 73% of participants had objective CIGH on motility testing, while only 26% of participants self-reported constipation.[58] When patients were asked to fill out a questionnaire that had the Rome criteria incorporated, 54% scored positively for CIGH and the sensitivity increased to 48%.[58] However, even with the Rome criteria incorporated, the majority of cases with CIGH were still missed and therefore, the tests can create false reassurance.

In contrast, validated gastrointestinal motility tests, such as using radiopaque markers, can provide accurate measures of gastrointestinal transit, but these tests are usually expensive, time-consuming and require specialist equipment and expertise. Furthermore, these tests measure gastrointestinal transit at only one point in time, while gastrointestinal motility varies over time and therefore transit needs to be considered regularly, particularly after increases in clozapine dose or serum level.[59] For these reasons, gastrointestinal motility tests are not very practical for the identification and monitoring of CIGH. Because screening for symptomatic constipation is of dubious utility, repeated measures of bowel motility are impractical and CIGH is so prevalent, Every-Palmer et al. recommend that a prophylactic laxative (or similar low-risk intervention) should be considered for all people taking clozapine.[58]

For additional support in diagnosing constipation, it may be considered to supply patients with a stool diary,[9,27,56] which may help in assessing the defaecation pattern in a more objective manner. An example for such an evaluation diary, based on the Bristol Stool Form Scale (BSFS),[60] is supplied in
It is advised to start the use of a stool diary before commencing clozapine treatment in order to obtain a baseline reference, and perform regular reviews – for instance, daily during the first four weeks and weekly/monthly thereafter – during treatment.

Prophylactic laxatives
Although it may seem that slow colonic transit times would translate into symptoms of constipation, it was shown that colonic hypomotility is much more frequent,[38] and constipation may be a poor predictor for severe complications such as paralytic ileus.[16] The article authors argued that, since there is no monitoring protocol which has proven to be effective in detecting colonic hypomotility, and the prevalence of hypomotility is high, all patients should be started on prophylactic laxatives.[38,55] However, one study found that only 6 out of 70 patients (9%) with reported severe constipation were prescribed prophylactic laxatives.[10]

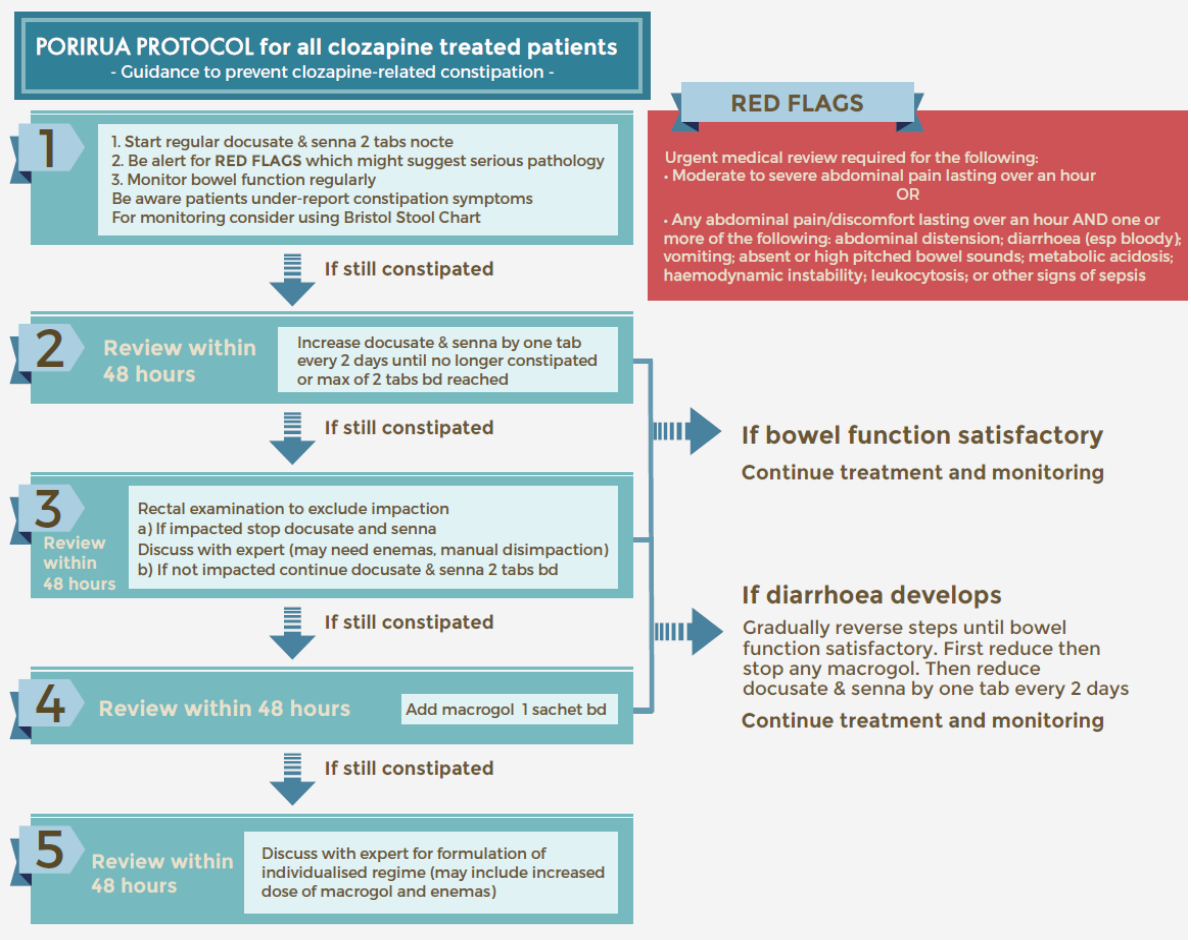
Table 3 shows an overview of laxatives, their characteristics and their usefulness in treating clozapine-induced constipation. In addition to changes in lifestyle, diet and concomitant medication, the addition of fibre supplements or other bulkforming agents can be considered first as preventive measures, followed by osmotic laxatives if necessary. If these strategies fail, stimulant laxatives, enemas and prokinetic drugs should be considered.[20]

Table 3. Treatment options for general constipation

Type	Action	Examples	Role in clozapine-induced constipation
Bulk laxatives	Increase stool bulk when taken with water	- Psyllium - Calcium polycarbophil - Bran - Methylcellulose	Preventive measure, insufficient to resolve established constipation. Should not be used in patients with obstructive symptoms or colonic dilatation[16,20]
Stool softeners	Allow water to be drawn into the bowel	- Docusate sodium - Ispaghula husk	Should be used in combination with stimulant laxative when treating established constipation
Osmotic laxatives	Hypertonic increase in stool water	- Polyethylene glycol (PEG) (i.e. macrogol) - Lactulose - Milk of magnesia - Sorbitol	Should be used in combination with stimulant laxative when treating established constipation
Stimulant laxatives	Increase gastrointestinal motility	- Bisacodyl - Sodium picosulfate - Senna	First line when treating established constipation, usually in combination with osmotic laxative or stool softener
Prokinetic agents	Increase gastrointestinal motility	- Prucalopride - Lubiprostone - Linaclotide	Can be tried when conventional laxatives fail[61–64]
Cholinergic agonists	May counteract clozapine's anticholinergic effects	- Bethanechol	May be considered in treatment-resistant constipation. Should only be used in consultation with gastroenterologist[37,65]

Every-Palmer et al. tested the effectivity of prophylactic senna and docusate in clozapine patients, with as a main readout the colonic transit time, measured with a radiopaque marker method.[28] If senna and docusate were ineffective, or impaction was established during rectal examination, macrogol was added. In case of impaction, senna and docusate were stopped. This approach, summarised in the Porirua Protocol (Image 1), reduced the colonic transit time substantially, from a median of 110 to 62 hours. The prevalence of hypomotility reduced from 86% to 50%, and the prevalence of severe gastrointestinal hypomotility was reduced from 64% to 21%.[28] The efficacy of this Porirua Protocol, which is used by their local services but is publicly available,[66] also seems promising based on internal audits performed 5 years before and 5 years after implementation: the prevalence of serious CIGH decreased from 8.2 per 100 person-years (95% CI 5.1-12.6) to 1.1 per 100 person-years (95% CI 0.2-3.1), respectively.

Image 1. The Porirua Protocol[66]



When constipation occurs

When a clozapine-treated patient develops constipation, abdominal examination is indicated.[27] Although clozapine is the most likely reason of constipation during clozapine therapy, it is important to make a full assessment of the patient's condition, and to also exclude causes of constipation other than clozapine.[20] For instance, colorectal cancer should be excluded in all patients older than 50 years who report a change in bowel habit.[20]

If intestinal obstruction can be excluded, the patient should be treated instantly with an appropriate laxative regimen (see Image 1 and Table 3 above). If not done already, other medication that can cause constipation (e.g. opiates, anticholinergics) should be discontinued, if possible.

A reduction in clozapine dose, if possible, may also be helpful,[67,68] but should not be regarded as treatment. In case augmentation is necessary following a dose reduction, amisulpride and aripiprazole have been found to have low risk of ileus[12] due to low or no muscarinic affinity, respectively.

Patients who have acute onset of symptoms, have severe symptoms, or who are not responding to treatment need referring to a specialist for further investigation.[27] Again, pay attention to warning signs such as abdominal pain, abdominal dilation, vomiting, overflow diarrhoea, absent or high-pitched bowel sounds and signs of sepsis.[27,28]

Treatment options in established clozapine-induced constipation
To our knowledge, there are no useful comparative clinical studies published on the effectiveness of different treatment regimens for clozapine-induced constipation.[9,69]
In a Belgian retrospective review of treatment strategies to resolve constipation induced by antipsychotics, 36.3% of 273 patients had at least one new pharmacological intervention for constipation. The most frequently used drugs were polyethylene glycols (PEG) macrogol 4000 (30.6%) and 3350 (22.5%) followed by the stimulant laxative sodium picosulphate (25.4%). These 3 constituted 75% of all drugs used to combat constipation.[70] In the UK, senna (55%), lactulose (50%), macrogols (16%), ispaghula husk (11%) and docusate (7%) were the most commonly used laxatives by 35% of the 202 investigated patients on clozapine. Among the patients on laxatives, 32% were concurrently prescribed two laxatives and 7% were prescribed three laxatives.[42] The effectiveness, however, was not addressed in both of these studies.

The *Maudsley Prescribing Guidelines* advises to use stool-softening laxatives and stimulants in combination in case of any signs of constipation induced by clozapine.[71] The combination of senna and docusate has proven to be effective in decreasing colon transit time.[28] Lactulose and polyethylene glycol (PEG/macrogol) may be considered second line options or alternatives, but preferably in combination with an agent that increases gastrointestinal motility. Based on in vitro data, cholinergic or serotonergic drugs may be helpful to combat clozapine-induced constipation, whereas opioid antagonists like methylnaltrexone are unlikely to be effective.[14] Although conflicting data and opinions appeared in the past on the long-term use of stimulant laxatives, its chronic use is probably safe as long as they are appropriately dosed.[28,72,73]

The newer drugs lubiprostone, bethanechol, prucalopride and linaclotide have shown some promise in case reports in clozapine-induced constipation unresponsive to conventional laxatives.[37,46,61–65]
Lubiprostone is suggested to have therapeutic benefit when it is added to a regimen that includes other laxatives, but its effectiveness as monotherapy is unassessed.[64] Although lubiprostone has few adverse reactions, generally limited to diarrhoea, nausea and headache, its use in clinical practice is limited due to the wide accessibility of significantly cheaper and generally effective laxatives.[46,74]
Bethanechol, however, should be used with caution, probably only in patients with severe clozapine-induced constipation who have failed to respond to aggressive treatment with conventional laxatives.[65]

Prucalopride is a 5-HT4 receptor agonist that was found to be effective as monotherapy in treating clozapine-induced constipation in an open-label, head-to-head comparison study.[63] Patients with ≤2 spontaneous bowel movements per week received 2 mg/day prucalopride and the proportion of patients with ≥3 spontaneous bowel movements increased in the following weeks, from 71.4% during week 1 to 85.7% at the end of week 4.[63] Prucalopride has a favourable safety profile with no apparent cardiac events, in contrast to other 5-HT4 agonists.[61] Adverse events that were reported during the open-label study included abdominal pain, headache and loose stool, but these adverse events were usually transient and subsided over a few days.[63]
Finally, linaclotide is a peptide that activates guanylate cyclase C and thereby augments the intestinal secretion. A case report describing one patient with severe clozapine-induced constipation and repeated episodes of ileus reported that the addition of linaclotide to a treatment regimen resulted in frequent and solid stools.[37].

A pilot study reported that the laxative properties of apple vinegar might also decrease the severity of clozapine-induced constipation.[75] However, due to a small sample size (n = 9) and patients self-reporting constipation severity (using a questionnaire) and treatment adherence, the reliability of the

results may be low. Therefore, the use of apple vinegar to prevent or treat clozapine-induced constipation should not be considered yet.

Bulkforming agents
Bulk laxatives may be of some use in the prevention of constipation, but they are not considered to be effective in treating it. So if constipation is recognised, pharmacological treatment from other classes of laxatives is needed.[16,27,53] Preventive bulkforming agents should only be prescribed in patients capable to follow the instructions to drink sufficient amounts of water. With insufficient fluid intake, bulkforming agents will contribute to constipation rather than ameliorating it.[55] In patients with obstructive symptoms or colonic dilatation, bulk laxatives and fibre supplementation should be avoided.[16,20]

Serious motility impairment of the gastrointestinal system
Severe constipation needs to be managed but does not generally warrant clozapine discontinuation.[76] However, in case of serious motility impairment of the gastrointestinal system, such as intestinal obstruction, faecal impaction and paralytic ileus, clozapine use and other likely causative medication should be stopped immediately[76] and the condition needs to be treated instantly by a specialist consultant. In almost all literature reports on severe gastrointestinal hypomotility, clozapine was indeed stopped.[77] Only in some reports,[67,68,78] the problem resolved after clozapine dose reductions and treatment of the condition.
In the event of life-threatening constipation, it is essential that the patient's fluid and electrolyte balance is maintained; if the patient is nil by mouth, IV isotonic fluid should be administered and vital organs need to be supported. Only in case of incomplete obstruction, decompression by nasogastric tube for the small intestines or colonoscopy for the colon should be attempted. Antibiotic therapy should be started when an infection is detected or prophylactically administered when there is immediate risk of infection. Urgent surgery is required when no adequate response is obtained in response to conservative measures within 48 hours, and/or when the patient is clinically unstable, has abdominal sepsis or has a complete obstruction.[23]

Constipation in the elderly
Elderly patients are more prone to develop clozapine-induced constipation, not only because they are more sensitive to clozapine's anticholinergic actions, but also due to risk factors intrinsic to the elderly population.[20,79] Parkinson's disease is also associated with a higher prevalence of constipation.[79] The use of prophylactic laxatives should be considered in elderly patients on clozapine, especially when other risk factors are present.

Rechallenges after gastrointestinal hypomotility
Clozapine is among the drugs for which constipation is a very common side effect. If it is possible to treat the patient with antipsychotics with lower potential to cause such effects, such as risperidone, ziprasidone and aripiprazole,[25] this would be advisable. However, patients who are otherwise resistant to treatment may need to restart clozapine treatment. A review by Nielsen et al. states that clozapine discontinuation with potential rechallenge is possible for ileus or subileus, provided there is appropriate surveillance and management, or prophylactic therapy.[76] It is important to note though, that a patient who has suffered from these conditions needs to be recovered completely before restarting clozapine treatment. As stated before, existing paralytic ileus is a contraindication for clozapine use, but a medical history is not.[17]

There are several case reports addressing re-initiation of clozapine treatment following severe clozapine-associated gastrointestinal hypomotility. Table 4 gives an overview of these publications,

including the preventive measures that were taken to prevent recurring gastrointestinal hypomotility. In summary of this information, it is advisable to follow preventive procedures such as described previously in this document. In addition, intensified monitoring, the use of prophylactic laxatives and clozapine dose reductions are advisable. Routine clozapine plasma level monitoring should be considered, as this may help preventing high levels of clozapine, and thereby reducing the risk of constipation. If the patient is considered to be unable to report symptoms of constipation, periodical abdominal physical examination and abdominal X-ray may be considered.

Table 4. Rechallenges after gastrointestinal hypomotility

Publication	Clinical findings	Rechallenge successful	Preventive measures
Van Haaren *et al.*[35]	Paralytic ileus, sigmoid volvulus, small bowel volvulus	No. Patient died due to returning ileus post-operatively	Re-challenge with clozapine on basis of blood level
Torrico *et al.*[64]	Large colonic faecal matter, concern for possible obstruction	Yes	Four laxatives: lubiprostone, polyethylene glycol, lactulose and docusate-senna.
Patel *et al.*[80]	Constipation; stool throughout colon without distension/obstruction	Yes; not stopped	Magnesium citrate enema; bowel transit returned to normal within 6 hours
Tomulescu *et al.*[37]	Paralytic ileus, small bowel volvulus	Yes	Clozapine dose reduction, potentiated with paliperidone. Treatment with bethanechol and linaclotide as laxatives.
Osterman et al. [81]	Hypoxic respiratory failure caused by aspiration of faeculent emesis due to impacted stool throughout his colon.	No. Patient died within a week after restart due to septic shock secondary to acute gastrointestinal necrosis	Oral laxatives while in hospital, unknown whether continued after discharge. Restarted on clozapine 100 mg twice daily after resolution of constipation on outpatient basis.
Castillo-García *et al.*[82]	Paralytic ileus	Yes	Oral laxative treatment and lifestyle Modifications
Osseis et al.[83]	Hepatic outflow block secondary to compression of the liver by a distended colon upstream of an impacted faecaloma.	Yes	Not mentioned.
Meyer et al.[46]	Small bowel obstruction, and ischemic small bowel	Yes	Lubiprostone treatment, along with lactulose and docusate. Clozapine dose reduction
Galappathie and Khan[84]	Marked colonic dilation from sigmoid to caecum, faecal impaction. Neostigmine and repeated enemas.	Yes	Gradual restart of clozapine after recovery and unsuccessful trials of alternative antipsychotics.
Poetter *et al.*[65]	Partial small bowel obstruction	Yes, at second try with bethanechol	Conventional laxatives supplemented with muscarinic stimulant bethanechol

Ikai *et al.*[77]	Focal phlegmonous appendicitis with advanced peritonitis and colon perforation. Appendectomy and intraperitoneal drainage	Yes	Gradual clozapine titration in the presence of laxatives (sennoside, magnesium oxide, and daikenchuto) and breath control exercises. Dose reduction. Weekly abdominal physical examination and monthly abdominal X-rays for the first 4 months
Dahmen *et al.*[85]	Bowel obstruction; total abdominal colectomy with ileosigmoid anastomosis	Yes	Monitoring of the patient's bowel movement, instructing patient on the use of milk of magnesia
McKinnon *et al.*[86]	History of multiple bowel surgeries; ileostomy. Bowel infarction, secondary to faecal dilatation. Bowel resection.	Yes	Notifying treatment team of potential dangers, severe dose reduction
Rege *et al.*[87]	Severe faecal impaction and sepsis	No	Concurrent use of laxatives (lactulose and docusate sodium/senna), dose reduction
Leong *et al.* [88]	Necrotising colitis; right hemicolectomy without primary anastomosis	Yes	Not mentioned
Rondla and Crane[67]	Paralytic ileus	Yes; not stopped	Dose reduction from 600 to 450 mg clozapine
Seller *et al.*[52]	Faecal impaction	Yes	Slow increase in dosage and attention was paid to proper diet and stool patterns.

Advice for daily practice:

- Discuss the risk of constipation before starting clozapine treatment and provide the patient with appropriate lifestyle advice on diet, fluid intake and exercise. Fibre supplementation and prophylactic laxatives may be considered in any patient starting clozapine.
- Assess pre-existing risk factors for constipation, and avoid concomitant medication known to cause constipation as much as possible.
- Actively and systematically screen and monitor for symptoms of constipation. Be aware that subjective reporting of gastrointestinal symptoms by patients on clozapine might not be an accurate indicator of the severity of constipation due to reduced intestinal nociception.
- In case of any signs of constipation, a stimulant laxative in combination with a stool softener (and/or osmotic laxative) is recommended as first-line treatment. Other classes of laxatives (except bulkforming laxatives) can be tried when conventional laxatives fail. Clozapine dose reductions may also help to ameliorate constipation.

- Be aware of warning signs indicative for serious constipation:
  - Abdominal pain
  - Abdominal dilation
  - Vomiting
  - Overflow diarrhoea
  - Absent or high-pitched bowel sounds
  - Signs of sepsis
- In case of serious motility impairment of the gastrointestinal system, the patient needs to be referred to a specialist, and clozapine use should be stopped immediately.
- If alternative antipsychotics are not an option, the patient can restart clozapine, but preventive measures should be taken.

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Appendix 1. Stool diary

Example of a stool diary according to the Bristol Stool Form Scale. It is advised to fill in this diary prior to starting clozapine treatment, to facilitate the timely recognition of stool changes.

Bristol Stool Form Scale (BSFS)						
Type 1 	**Type 2** 	**Type 3** 	**Type 4** 	**Type 5** 	**Type 6** 	**Type 7** 
Hard lumps	Sausage-shaped, lumpy	Sausage, cracks on surface	Sausage, smooth and soft	Soft blobs, clear-cut edges	Fluffy pieces, ragged edges	Watery, no solid pieces

Week …	**Date**	**Time**	**BSFS Type** (1-7, see above)	**Straining**	**Incomplete passage of stool**	**Pain** (location)	**Needed help to empty**	**Feeling as if blocked**
Monday								
Tuesday								
Wednesday								
Thursday								
Friday								
Saturday								
Sunday								