Clozapine: why wait to start a laxative?

ARTICLE

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SUMMARY

Clozapine, the antipsychotic of choice for treatment-resistant schizophrenia, has a number of side-effects, some of which are potentially life-threatening. Historically viewed as a relatively minor side-effect, there is increasing awareness of the potentially severe sequalae of constipation secondary to clozapine-induced gastrointestinal hypomotility (CIGH). These include ileus, intestinal obstruction, bowel ischaemia, gastrointestinal necrosis, toxic megacolon and death. CIGH is significantly more common than clozapine-induced blood dyscrasias and has a higher mortality rate. Although strict criteria must be followed to assertively monitor, detect and treat blood dyscrasias in patients taking clozapine, no such framework exists for CIGH. We recommend that prescribing guidelines, regulatory agencies and information from manufacturers should more clearly highlight the risks identified in the literature. Furthermore, we recommend that, in people taking clozapine, constipation should be prevented by prophylactic treatment with laxatives rather than treated only when clinically identified.

LEARNING OBJECTIVES:

After reading this article you will be able to:

- understand the mechanism of gastrointestinal hypomotility in those taking clozapine
- improve the monitoring of clozapine-induced constipation
- understand prophylactic laxative treatment and the use of less commonly prescribed laxatives in patients who experience clozapine-induced constipation.

DECLARATION OF INTEREST:

None.

KEYWORDS

Drug interactions and side-effects; clozapine; clozapine-induced hypomotility; in-patient treatment; community mental health teams.

Clozapine remains the gold-standard antipsychotic for treatment-resistant schizophrenia, but its use comes with a significant number of potentially life-threatening side-effects (Taylor 2017). Among the most prominent of these are blood dyscrasias, diabetic ketoacidosis and myocarditis, for each of which there are strictly enforced monitoring guidelines (Cohen 2012). Clozapine can also cause constipation (the difficult, incomplete or infrequent evacuation of dry hardened faeces), which affects 30–60% of patients (De Hert 2011a; Shirazi 2016; Taylor 2019; also, clozapine SmPC: Box 1).

Historically, clinicians have viewed antipsychotic-induced constipation as a troublesome but mild adverse effect of antipsychotic therapy. However, today we are overwhelmed with evidence that constipation can in fact lead to ileus, intestinal obstruction, bowel ischaemia, gastrointestinal necrosis or toxic megacolon, the consequences of which can be fatal (Schwartz 1993; Erickson 1995; Hayes 1995; Drew 1997; Levin 2002; Townsend 2006; Rondla 2007; Palmer 2008; Hibbard 2009; De Hert 2011a; Flanagan 2011; Nielsen 2012; Oke 2015; Every-Palmer 2017a; West 2017).

Constipation caused by clozapine-induced gastrointestinal hypomotility (CIGH) is much more common than clozapine-induced blood dyscrasias and has a higher mortality rate (Cohen 2012; Every-Palmer 2016; Ingimarsson 2018). When prescribing clozapine, strict criteria must be followed to assertively monitor, detect and treat related blood dyscrasias (clozapine SmPC: Box 1). No such framework exists for the monitoring of constipation, even though CIGH may also lead to death. In a recent and large pharmacovigilance study in Australia and New Zealand, 160 patients (37/10 000) on clozapine were reported as having serious gastrointestinal hypomotility. Of these, 29 (7/10 000) are known to have died – a fatality rate of 18% (Every-Palmer 2017a). The case-fatality rate reported by the US Food and Drug Administration (De Hert 2011b) was nearly identical to this, at 21.9% (7 of 32 patients). Despite the prevalence and significant mortality associated with CIGH, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK does not mention CIGH specifically in its drug information for prescribers (clozaril: http://www.mhra.gov.uk/spc-pil/); rather, the summary of product characteristics for the drug lists intestinal obstruction/paralytic ileus/faecal impaction as 'very rare' (Clozapine SmPC last

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accessed 2019). The term 'very rare' is defined as 'isolated case reports or occurring in less than one in 10 000 users'.

Aside from the fatal consequence of constipation caused by CIGH, it has been repeatedly shown that chronic constipation can have a negative impact on the patient's quality of life (Damon 2004; Dennison 2005; Wald 2007). Symptoms of delayed colonic transit time include reduced frequency of defecation, lack of urgency to defecate, abdominal distension, bloating and feelings of incomplete evacuation (Koch 1997). One study reported that median colonic transit time for patients prescribed clozapine was 104.5 h, which is over four times longer than for those on other antipsychotics (23 h; $P < 0.0001$) (Every-Palmer 2016). Eighty per cent of clozapine-treated patients had colonic hypomotility, compared with none of those treated with other antipsychotics (olanzapine, risperidone, paliperidone, aripiprazole, zuclopenthixol or haloperidol).

This article will highlight the need for enhanced identification and treatment of constipation associated with clozapine and will challenge the status quo of reserving treatment for patients with identified or reported clozapine-induced constipation. We will emphasise the importance of prophylactic use of laxatives in patients who are taking clozapine, describing both commonly prescribed laxatives and less well-known agents.

Despite the recommendation that monitoring and treatment of constipation caused by CIGH should be brought in line with the strict framework in place to detect blood dyscrasias (Cohen 2012), there has been no such coordinated provision. Although we uphold the need for a systematised approach to monitoring clozapine-induced constipation, we recommend interim improvement to local practice.

Given the life-threatening severe nature of severe clozapine-induced constipation, readers' attention is drawn to Box 2, which lists symptoms of suspected acute CIGH. A low threshold for referral to an emergency department is warranted, as there are cases in which death occurred only hours after the first symptom was reported and the patient had no previous symptoms of constipation.

Risk factors for constipation in schizophrenia

People with schizophrenia typically have pre-existing risk factors for constipation: a sedentary lifestyle, obesity, poor diet, reduced fibre intake and dehydration, to name but a few. Prospectively identifying individuals who are suffering from constipation caused by CIGH is further limited as symptoms are often not reported and are not easily objectively recognised by clinicians, given the private nature of patients' bowel functions. Patient under-reporting could also be due to inherent cognitive deficits, core symptoms of schizophrenia, reduced pain sensitivity or reduced ability to communicate (Bickerstaff 1988; Dworkin 1994; De Hert 2011c; Stubbs 2015). Clozapine itself causes side-effects that can exacerbate such pre-existing risk factors: sedation (through antihistaminergic properties), increased appetite and hypersalivation (which can worsen dehydration) (clozaril at http://www.mhra.gov.uk/spc-pil/; clozapine SmPC: Box 1). Clozapine is thought to reduce gastrointestinal motility through its gut peripheral muscarinic anticholinergic effects and antagonism at serotonin receptors (Meltzer 1991; Chengappa 2000; Crowell 2001; Abrams 2006). These multifaceted risk factors for constipation – schizophrenia itself, inherent under-reporting and under-detection, clozapine side-effects, together with reduced gastric motility – put this subgroup of patients at a degree of risk that necessitates either a challenge to the ethics behind most current 'wait and treat' constipation guidance or an overhaul of the way clinicians view the prescribing of laxatives.

Opinions differ about the relationship between clozapine dose, plasma levels and rates of CIGH or ileus. A subgroup analysis in a 22-year bi-national pharmacovigilance study in Australia and New Zealand showed that those with fatal outcomes had significantly longer duration of clozapine treatment (median 4.2 years, IQR = 1.5–8.6 years) than the rest of the group (median 1.9 years, IQR = 0.2–5 years) (Every-Palmer 2017a). The odds ratio of a fatal outcome increased by 1.21 years (95% CI 1.02–1.44) for every 2 years on clozapine. Age, female gender, dose and receiving other constipating medications had a positive, but non-significant association with fatal outcomes. A study focusing on ileus alone (Nielsen 2012) found an increased risk with increasing age (OR = 1.03, 95% CI 1.01–1.04), female gender (OR = 1.60, 95% CI 1.10–1.23) and duration of clozapine treatment (OR = 1.99, 95% CI 1.21–3.29). The onset of ileus occurred on average more than 3 years after the prescription of the offending drug, and a recent Icelandic study (Ingimarsson 2018) found a mean time to ileus of 13.7 years. However, a review of the literature (West 2017) lists risk factors for CIGH as older age, male gender, the first 4 months of treatment, co-prescription of constipating agents, higher doses and previous CIGH. Given the conflicting results in the literature, identifying patients who are at a higher risk of developing CIGH or more sinister gastrointestinal complications such as ileus remains challenging.

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BOX 1 Summaries of product characteristics (SmPCs)

On the electronic Medicines Compendium (eMC), searching for drugs under their generic names often retrieves the proprietary brands available in the UK. The SmPCs listed below are for generic or example proprietary brands. All urls shown were accessed in March 2019.

Clozapine: Clozaril 25mg tablets (https://www.medicines.org.uk/emc/product/4411/smpc)

Lactulose: Duphalac (https://www.medicines.org.uk/emc/product/5525/smpc)

Macrogols (polyethylene gycols): Movicol Plain 13.7 g sachet, powder for oral solution (https://www.medicines.org.uk/emc/product/257/smpc)

Orlistat: (https://www.medicines.org.uk/emc/product/8703/smpc)

Senna: (https://www.medicines.org.uk/emc/product/9458/smpc)

Sodium docusate: Dulcoease 100 mg capsules (https://www.medicines.org.uk/emc/product/212/smpc)

Sodium picosulfate: Dulcolax (https://www.medicines.org.uk/emc/product/905/smpc)

Long-term prophylactic and post-CIGH use of laxatives: limitations and side-effects

It is important to be aware of the limitations of prophylactic laxatives in completely eradicating gastrointestinal side-effects associated with clozapine, for example they will most likely have no effect in eliminating the risk of colitis or bowel ischaemia (Shammi 1997; Karmacharya 2005; Leong 2007; Foxx-Orenstein 2008; McKinnon 2009; Yu 2013). There are also potential side-effects related to long-term prophylactic use, which we describe in more detail later in this article. Despite this, and in support of other authors (Every-Palmer 2014, 2017a, 2017b), we propose prophylactically treating all patients on clozapine, because the risks of not treating far outweigh the benefits of a 'wait and treat' practice. Table 1 summarises current practice in the prevention of clozapine-induced constipation and outlines suggested improvements.

BOX 2 Warning signs of acute clozapine-induced gastrointestinal hypomotility (CIGH)

Seek urgent medical review if any of the following symptoms occur:

- moderate or severe abdominal pain lasting over an hour
- abdominal distension
- vomiting
- overflow diarrhoea or bloody diarrhoea
- absent or high-pitched bowel sounds
- metabolic acidosis
- haemodynamic instability
- leukocytosis
- signs of sepsis

These symptoms are signs of suspected acute CIGH, and a low threshold for referral to A&E is warranted as death can occur within hours.

Re-introducing clozapine in a patient following a potentially fatal side-effect is never without risk. Therefore, prophylactic laxatives at appropriate doses, along with dietary and lifestyle changes highlighted in Table 1, are recommended when re-introducing clozapine in a patient with a history of clozapine-induced constipation or CIGH. Cases of successful clozapine re-challenge following bowel perforation and bowel infarction, with notably smaller doses of clozapine alongside many lifestyle changes and closer monitoring of bowel habits, have been reported (McKinnon 2009; Ikai 2013).

Classes of laxative

Intervention protocols such as that published by the Cochrane Collaboration (Every-Palmer 2014) offer useful advice on the different laxatives, and in Table 2 we give a summary of those that are currently available in the UK, including lesser-known medications that have been used in specialist situations by consultant psychiatrists during clozapine re-challenge following CIGH.

Laxative agents are typically broken down into four separate classes, namely bulking agents, osmotic agents, lubricants and stimulants. It is generally accepted that the first three classes are thought to be safe in long-term use.

Bulking agents

Bulking agents act by virtue of their water retaining properties, leading to increased gut motility; however, overdosage of bulk-forming laxatives or significant dehydration can result in faecal impaction and bowel obstruction. Adverse effects of bulk-forming laxatives, even in chronic use, are infrequent but psyllium, the plant-based fibre

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TABLE 1 **Prevention of clozapine-induced constipation: current practice and suggested improvements**[a]

Before commencing clozapine		
Actions/factors for consideration	**Current practice**	**Suggested improvements**
Identify risk factors associated with increased risk of constipation (NPC 2011; NICE 2017)	Try to address modifiable risk factors: • recommend increased fluid intake • advise on change in diet (consider high fibre) • recommend increased activity • review co-prescribed medication in coordination with GP or clinical pharmacist	Consider starting a food and fluid chart
Question the patient to rule out gastrointestinal history and conduct a physical examination to identify current constipation	Do not initiate clozapine if patient is currently constipated	Treat constipation: consider the patient's previous response to laxative treatments Consider a stool diary or doing a stool chart (e.g. the BSC) after constipation (if any) has been treated and as a baseline for the patient before commencing clozapine. This may be done by the patient or may need to be done by the care team, depending on the patient's presentation
Initiation of clozapine (first 17 weeks) in UK practice		
Actions/factors for consideration	**Current practice**	**Suggested improvements**
Clozapine titration should at the very least be in line with the SmPC	If the patient presents with constipation a slower increase may be considered (by 25 mg/day or 100 mg/week) (Hayes 1995)	
Clozapine may cause sedation, anticholinergic side-effects, hypersalivation and increased appetite, which increase the risk of constipation (clozapine SmPC: Box 1)	It is recommended that modifiable risk factors are addressed, in coordination with GP and/or pharmacist if necessary, to reduce the risk of developing constipation	Proactively address modifiable risk factors (this will obviously depend on the patient's mental state): • Consider increasing fibre in diet by 20–25 g/day to achieve the recommendations (in UK, 30 g/day). This may help increase stool weight and decrease gastric transit time (Muller-Lissner 1988; Young 1998; Fitzsimons 2005) • Consider increasing fluid intake to the usual recommendation of 1.5–2 l a day. This is especially important if increasing fibre intake, as increasing fibre without adequate fluid may lead to bowel obstruction (Hayes 1995; Young 1998; Fitzsimons 2005; De Hert 2011a) • Consider decreasing sedentary lifestyle and increasing active time to the recommended 150 min a week (Young 1998; Fitzsimons 2005; NHS 2013)
Consider using an adverse-effects scale that specifically questions constipation	The GASS is most commonly used with patients on clozapine. This encourages establishing baseline bowel functioning before initiation of clozapine and subsequent routine monitoring against this baseline for the possible development of constipation (other scales include Rome IV and SMARTS) If constipation develops, treatment with laxatives based on the patients' previous response to laxative therapy is recommended (NPC 2011; NICE 2017)	As well as using an adverse-effects scale that specifically questions constipation, continue to use a stool chart (e.g. the BSC) for the first 4 weeks of therapy Compare this with the baseline stool diary: if there is a change in stool or bowel habits or fewer than three bowel movements in a week, consider referral for medical abdominal examination
Start the patient on laxatives if a reduction in the frequency of bowel opening occurs. The choice of laxative should be driven by the patient's previous response to laxative therapy (NPC 2011; NICE 2017)		Consider starting all patients on both a regular prophylaxis stool softener and a stimulant laxative: • sodium docusate 100 mg 3 times a day (max 500 mg a day) (sodium docusate SmPC: Box 1) • macrogol 1 sachet up to twice daily (magrogols SmPC: Box 1) • senna 2 tablets, once daily (senna SmPC: Box 1) The choice of laxative here is to specifically increase the stimulation of the gut and reduce the surface tension of the stool, thus reducing the likelihood of constipation caused by CIGH (NPC 2011; Every-Palmer 2014, 2017b; NICE 2017; Ducrotté 2017; Muller-Lissner 2017) If bowel function is satisfactory with the prescription of laxatives, continue with titration and prescription.

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(*Continued*)

Clozapine treatment at the effective dose		
Actions/factors for consideration	**Current practice**	**Suggested improvements**
Clozapine treatment at the effective dose Actions/factors for consideration	Current practice	Suggested improvements
Consider using an adverse-effects scale that specifically questions constipation	The GASS is most commonly used with patients on clozapine . It is usually administered during the visit to the community clinic either fortnightly or monthly, depending on the frequency of full blood test monitoring requirements If constipation develops, treatment with laxatives based on the patient's previous response to laxative therapy is recommended (NPC 2011; NICE 2017)	In addition to the use of an adverse-effects scale that monitors for constipation, continue with a stool chart but reduce stool chart monitoring to fortnightly or monthly It is important to bear in mind evidence that the risk of fatal outcome due to CIGH increases for every 2 years the patient is treated with clozapine (Every-Palmer 2017a) Continue with the prophylactic use of a stool softener and stimulant laxative. If diarrhoea develops, consider reducing the regular laxatives (once overflow diarrhoea due to chronic constipation has been ruled out). Hypokalaemia secondary to diarrhoea may occur, so we strongly recommend monitoring urea and electrolytes If reducing laxatives, it is important to continually monitor for the development of constipation. Once bowel function returns to normal, consider restarting prophylactic stool softener and stimulant laxatives, with close monitoring for development of diarrhoea

Development of constipation		
Actions/factors for consideration	**Current practice**	**Suggested guidance**
Carry out rectal examination to rule out impaction (Young 1998; Fitzsimons 2005; BNF 2018)	If impacted, discuss with expert medical team. If not impacted, start laxative according to patient's previous response to laxative therapy (NPC 2011; NICE 2017; BNF 2018)	If suspected impaction, stop sodium docusate and senna and discuss with expert medical team If not impacted, consider reviewing the patient's adherence to regular laxative treatments. If non-adherent, re-start at previous doses
If after 48 h and there is still no bowel movement	Consider increasing the laxative dose. Consider adding Macrogol® or lactulose or consider a sodium picosulfate enema (Ducrotté 2017; Muller-Lissner 2017; BNF 2018; lactulose, macrogols and sodium picosulfate SmPCs: Box 1) It is important to bear in mind the required speed at which the laxative is required to work (e.g. lactulose will take 72 h to become fully effective) (lactulose SmPC: Box 1)	

BNF, British National Formulary; BSC, Bristol Stool Chart (Lewis 1997); GASS, Glasgow Antipsychotic Side-Effect Scale (Hynes 2015); GP, general practitioner; NICE, National Institute for Health and Care Excellence; NPC, National Prescribing Centre; Rome IV, the Rome IV Diagnostic Criteria for Functional Constipation (see Lacy 2016); SMARTS, Systematic Monitoring of Adverse Events Related to Treatments (Haddad 2014); SmPC, summary of product characteristics.
Sources: Koch *et al* (1997); Every-Palmer *et al* (2014, 2017a).
a. At all stages, clinicians should be alert for signs of acute CIGH (see Box 2). A low threshold for referral to an emergency department is warranted as death can occur within hours. This does not deviate from current recommended practice.

TABLE 2 **Summary of available laxatives used for constipation in the UK (including those less commonly prescribed following constipation caused by clozapine-induced gastrointestinal hypomotility)**

Treatment	Mechanism of action	Adult dose	Side-effects
Bulk-forming laxatives			
Ispaghula husk Methylcellulose Sterculia	Bulk-forming laxatives increase colonic intraluminal volume, producing a stretch reflex that stimulates gut motility	1 sachet mixed with 150 ml of water twice a day 3–6 tablets a day with 300 ml of water 1–2 sachets once or twice a day or 1–2 heaped 5 ml spoonful's once or twice a day	Bulk-forming laxatives are difficult to ingest, diarrhoea, gastrointestinal discomfort, nausea, the plant-based fibre found in many bulk-forming laxatives is a known allergen and case reports of anaphylactic reactions have been reported. Faecal impaction and bowel obstruction can occur if there has been over-dosage of the laxative or inadequate fluid intake
Osmotic agents			
Lactulose	Osmotic agents increase the amount of water in the large bowel either by drawing fluid from the body into the bowel or retaining the water administered with it, leading to modification of the stool consistency and increased faecal bulk	10–30 ml twice a day	Abdominal cramps, bloating, flatulence, diarrhoea
Macrogol 3350, with potassium chloride, sodium bicarbonate and sodium chloride		Half-strength sachets: dissolve each sachet in 62.5 m of water and take up to 6 sachets a day Full-strength sachets: dissolve each sachet in 125 ml of water and take up to 3 sachets daily	Flatulence, gastrointestinal discomfort, nausea and electrolyte imbalance (discontinue if this occurs). For osmotic agents, consider monitoring electrolytes (in particular magnesium) during the patient's required full blood count
Lubricants			
Arachis oil	These agents lubricate and softens stool by reducing the surface tension and prevents water reabsorption into the GI tract	130 ml given via enema (best to warm enema in water before use)	Contraindicated if allergic or hypersensitive to peanuts; depletion of fat-soluble vitamins is theoretically possible. Aspiration of mineral oils can lead to lipoid pneumonia, so these agents should not be used in people who are risk of aspiration
Liquid paraffin		10–30 ml orally at night	Depletion of fat-soluble vitamins is theoretically possible. As noted above, aspiration can lead to lipoid pneumonia
Sodium docusate		Up to 500 mg a day in divided doses	Abdominal cramps, nausea and rarely rash. As noted above, aspiration can lead to lipoid pneumonia
Stimulant laxatives			
Bisacodyl	Stimulant laxatives increase intestinal motility and secretion from fluid accumulation in the distal ileum and colon. They are also believed to stimulate the sensory nerve endings of the colonic mucosa	Orally 20 mg once a day, usually at night Rectally 10 mg suppository once a day	GI discomfort and nausea
Senna		7.5 mg–30 mg once at night	GI discomfort, skin reactions; monitor for hypokalaemia with prolonged use
Sodium picosulfate		Orally 5–10 mg once a day Rectally 1 enema every 12 h; each enema contains 21.4 g sodium dihydrogen phosphate dihydrate and 9.4 g disodium phosphate dodecahydrate	Diarrhoea, gastrointestinal discomfort
Less well-known agents tried during re-challenge of clozapine following suspected CIGH			
Lubiprostone	Bicyclic fatty acid derived from prostaglandin E1; it acts locally on chloride channels, enhancing chloride-rich intestinal fluid secretion	24 µg twice a day	Headache, nausea, diarrhoea
Orlistat	GI lipase inhibitor, used for its side-effects of faecal urgency and increased defecation	120 mg 2–3 times a day	Faecal urgency, faecal incontinence, increased defecation, oily spotting, abdominal pain, weight loss
Bethanechol	Synthetic choline ester of carbamic acid that possesses a significant acetylcholine-like activity and is used for its side-effect of increased defecation	10 mg 3 times a day	Nausea, vomiting and involuntary defecation

GI, gastrointestinal.
Sources: National Prescribing Centre (2011); Every-Palmer *et al* (2014); National Institute for Health and Care Excellence (2017); British National Formulary (2018).

found in many bulk-forming laxatives, is a known allergen and there are case reports of anaphylactic reactions (Vaswani 1996; Khalili 2003).

Given the primary mechanisms of clozapine-induced constipation, we would not recommend bulking agents as first-line treatment because of

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the risk of obstruction; this recommendation is in keeping with the Porirua protocol (Every-Palmer 2017b) and research findings (Meltzer 1991; Chengappa 2000; Crowell 2001; Abrams 2006).

Osmotic laxatives

Osmotic laxatives broadly work by drawing fluid into the bowel as well as promoting the retention of fluid in the lumen of the colon. Theoretically, the long-term use of such laxatives could lead to reduced absorption of fat-soluble minerals, although this has never been reported in the literature (Xing 2001). A potential serious side-effect is electrolyte imbalance as a result of excess ion absorption, particularly in patients with compromised renal function. Assessing electrolytes is an established procedure before commencing clozapine. For patients co-prescribed long-term osmotic laxatives, and we would suggest that clinicians also consider monitoring electrolytes and magnesium levels alongside the mandatory monthly full blood count (macrogols and lactulose SmPCs: Box 1).

Lubricant laxatives

Lubricant laxatives, often derived from liquid paraffin, decrease the absorption of water in the colon and act to soften the stool. Aspiration of such mineral oils can lead to lipoid pneumonia, highlighting that these agents should not be used in people who are risk of aspiration (Weinstein 2001). It is of course worth highlighting here the elevated risk of aspiration pneumonia with clozapine (Taylor 2019).

Stimulant laxatives

Stimulant laxatives increase intestinal motility and secretion from fluid accumulation in the distal ileum and colon. They are also believed to stimulate the sensory nerve endings of the colonic mucosa. Given the proposed mechanism of action of constipation caused by CIGH, these have been used prophylactically in the treatment of clozapine-induced constipation and prevention of CIGH (Every-Palmer 2017b; bisacodyl, senna and sodium picosulfate SmPCs: Box 1).

Less well-known laxatives

If lesser-known laxatives are to be tried at clozapine re-challenge, it is essential that the clinician is familiar with the laxative chosen.

Lubiprostone, a bicyclic fatty acid, has been used for chronic constipation and opioid-induced constipation in both men and women and for the treatment of irritable bowel syndrome with constipation in women (Wilson 2015). It has also been used successfully where other laxatives have failed in a clozapine re-challenge following CIGH (Meyer 2014).

Three case reports have shown that the side-effects of orlistat, a medication licensed for weight loss, led to the successful treatment of intractable opioid-induced constipation (Guarino 2005; orlistat SmPC: Box 1). In all three cases, the patient had not responded to bisacodyl, bulking agents, osmotic laxatives and senna, but orlistat 120 mg taken twice daily resulted in successful bowel management. A small randomised controlled trial involving individuals with clozapine-induced constipation thought to be due to CIGH reported a statistically significant improvement in the prevalence of constipation, diarrhoea and normal stools in those given orlistat for 16 weeks in comparison with placebo (Chukhin 2013). It is important to note, however, that 47 of the 54 patients also received conventional laxatives in addition to orlistat or placebo.

Bethanechol is a synthetic choline ester of carbamic acid which is licensed for use in urinary incontinence or reflux oesophagitis and has side-effects that include nausea, vomiting and involuntary defecation in overdose. Bethanechol 10 mg taken three times a day has been used to treat CIGH and was effective in reducing total amount of laxatives and enemas required to maintain regular bowel movements (Poetter 2013).

Long-term side-effects associated with the use of stimulant laxatives

Although the chronic use of bulking, osmotic and lubricant laxatives has long been considered safe, there has historically been concern about the risk attached to long-term use of stimulant laxatives such as senna (Leng-Peschlow 1992). This is of particular significance given our recommendations, in keeping with the Porirua protocol (Every-Palmer 2017b), for prophylactic use of senna and sodium docusate in those prescribed clozapine. Such concern has typically been focused on the potential for stimulant laxatives to cause structural changes in the colon that lead to intestinal dysmotility as well as the risk that chronic use might lead to the development of cathartic colon, melanosis coli or even, potentially, cancer. Stimulant laxatives exert direct toxic effects on the colonic mucosa, although this is of uncertain functional significance and is dependent on the weight percentage of sennosides in the preparation (Leng-Peschlow 1992; Xing 2001). The presence of neurotoxic compounds in preparations no longer available is thought to have influenced the conclusions of historical trials. From more recent research, there is no clear evidence that long-term use even of anthranoid-containing laxatives causes damage to the colonic myenteric system (Xing 2001). Further, there is no convincing

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evidence linking use of stimulant laxatives to cathartic colon, a radiological term describing loss of haustration and dilated lumen (Morales 2009).

First mentioned in 1829, melanosis coli describes the abnormal pigmentation of the colon by lipofuscin and so is perhaps better termed pseudo-melanosis coli. More recent literature highlights that this phenomenon is a non-specific marker of epithelial apoptosis with a variety of causes, including idiopathic constipation, carcinoma and stimulant-laxative use (Byers 1997). Although *in vitro* and animal studies suggest the potential carcinogenic effect of stimulant laxatives, the results of epidemiological studies in several countries have not supported this view. There is no robust evidence to suggest a link between chronic use of stimulant laxatives and the development of gastrointestinal tumours (Kune 1993; Nusko 2000; Xing 2001). Thus, the recent evidence suggests that the risks of chronic stimulant-laxative use have historically been overstated, which has potentially limited their use.

Should diarrhoea develop in the context of long-term use of a stimulant laxative there is a risk of hypokalaemia. We would therefore recommend ongoing monitoring of bowel habit change in patients taking clozapine and prophylactic laxatives and the cessation of laxatives, followed by clinical review, should diarrhoea occur.

Conclusions

Constipation is already more common in people with schizophrenia than in the general population, owing to multiple factors, including sedentary lifestyle, obesity, poor diet, reduced fibre intake and dehydration. Clozapine-induced gastrointestinal hypomobility (CIGH) leading to constipation is a common, and potentially life-threatening, side-effect in a population where this medication's use is often the only means of maintaining mental well-being. It is more common than blood dyscrasias and has a higher mortality rate. There is a lower likelihood that patients will report this side-effect. It is therefore imperative that CIGH and constipation are given a higher profile by regulatory agencies and that clozapine manufacturers' literature mirrors the most recent data. A more stringent monitoring framework in national and local prescribing guidelines is also warranted.

We recommend the routine use of adverse-effects rating scales that include constipation as a side-effect, the use of stool monitoring charts and the operation of a low threshold for the referral of patients on clozapine who develop constipation to specialist medical attention. We challenge the status quo of reserving laxative use for those patients with identified or reported clozapine-induced constipation. Given the prevalence of clozapine-induced constipation and the high mortality rate associated with this side-effect, we are of the view that it is ethically sound to present an alternative: prophylactic use of laxatives throughout the patient's entire treatment with clozapine. We recommend review of regular laxatives only if diarrhoea develops or a change in frequency of bowel movements necessitates their withdrawal. This is especially important for patients attending UK community clozapine clinics, where often clozapine treatment is managed by senior non-medical staff.

We acknowledge that, if this recommendation is followed, there will be a proportion of clozapine-treated patients prescribed laxatives who do not have constipation secondary to CIGH. However, when taking into consideration the fact that CIGH can occur at any time throughout the course of a patient's treatment with clozapine and can have a potentially fatal outcome, the safety of long-term laxative use, the recommendation to stop laxatives if diarrhoea develops and the latitude of clinicians to provide individualised care, we are of the clear view that prophylactic use of laxatives in patients taking clozapine is ethical. Similar prophylactic use of laxatives is considered ethical and appropriate in other situations, such as patients taking opioids (Bell 2009).

Existing protocols for the use of prophylactic laxative treatment recommend the first-line choice of sodium docusate or macrogol and senna, because of the reported pathological mechanism of CIGH. The risks of long-term stimulant laxative use have been overstated historically and we would correspondingly recommend their prophylactic use unless the patient develops diarrhoea. Monitoring of bowel-habit change in the context of long-term laxative use should be included in any protocols for their prophylactic use. The addition of regular electrolytes monitoring, including magnesium levels, should be considered when long-term osmotic laxatives are required.

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MCQs

Select the single best option for each question stem

1 Which of the following about the relationship between clozapine and gastrointestinal motility is false?

a clozapine is thought to reduce gastrointestinal motility through its effect on peripheral muscarinic acetylcholine receptors at gastrointestinal sites
b the relationship between clozapine and gastrointestinal motility is poorly understood
c clozapine is thought to reduce gastrointestinal motility through its agonistic effect on peripheral dopamine receptors at gastrointestinal sites
d clozapine is thought to reduce gastrointestinal motility through its antagonistic effect on serotonin receptors at peripheral gastrointestinal sites
e clozapine is thought to reduce gastrointestinal motility by causing hypersalivation.

2 In patients prescribed clozapine, median colonic transit time is:

a not affected by the antipsychotic
b quicker than with other antipsychotics
c over four times longer than with other antipsychotics
d twice as long as that with other antipsychotics
e twice as quick as that with other antipsychotics.

3 In terms of the gastrointestinal side-effects of clozapine, which of the following statements is false?

a constipation is much more common than blood dyscrasias
b clozapine-induced gastrointestinal hypomotility (CIGH) often leads to bowel ischaemia
c a recent study demonstrated a fatality rate of 18% among patients with severe CIGH
d CIGH has a higher mortality rate than clozapine-induced blood dyscrasias
e prophylactic laxatives may reduce the adverse consequences of CIGH.

4 Which of the following statements about people who take clozapine is false?

a symptoms of constipation are not easily recognised by clinicians
b a patient's under-reporting of constipation could be due to inherent cognitive deficits
c people with schizophrenia may have a reduced pain sensitivity
d most patients with schizophrenia will openly report symptoms of constipation
e people with schizophrenia may have a reduced ability to communicate.

5 Which of the following statements about the treatment of refractory constipation is false?

a lubiprostone has been used successfully to treat constipation in people who have previously experienced CIGH where other laxatives have failed
b the weight-loss agent orlistat may be helpful in treating intractable constipation
c there is little evidence to substantiate claims that anthranoid-containing laxatives such as senna lead to intestinal dysmotility
d using arachis oil may lead to depletion of fat-soluble vitamins
e bethanechol is ineffective in treating refractory constipation.