CLOZAPINE-INDUCED GASTROINTESTINAL HYPOMOTILITY (CIGH) MANAGEMENT

TARGET AUDIENCE	All staff involved in the prescribing, administration and supply of clozapine in NHS Lanarkshire
PATIENT GROUP	All patients prescribed clozapine in NHS Lanarkshire

Clinical Guidelines Summary

- Clozapine-induced gastrointestinal hypomotility (CIGH) is a common adverse effect of clozapine therapy.
- Complications relating to CIGH can be fatal.
- Individuals on clozapine should have proactive screening and monitoring of GI symptoms at every point of blood sampling.
- Individuals on clozapine should be counselled on risks of constipation and provided with suitable advice and information.
- Individuals on clozapine often need combinations of laxatives.
- Individuals on clozapine may have other risk factors for constipation which need taken into account and may require escalation of laxative therapy.
- All staff managing patients prescribed clozapine should be aware of severe signs and symptoms of CIGH requiring urgent interventions.
- An inpatient stay in hospital introduces potential risks that may exacerbate risk of CIGH.
- A break in treatment from clozapine may be indicated in the event of worsening GI symptoms.

Contents

1. Aim

To provide guidance to support the appropriate assessment of patients prescribed clozapine to promote the early identification and management of clozapine-induced gastrointestinal hypomotility and constipation.

2. Background

Around 80% of patients prescribed clozapine exhibit gastrointestinal (GI) hypomotility or 'slow gut'. This may occur at any point in the GI tract from oesophagus to rectum resulting in symptoms such as indigestion, dysphagia, abdominal cramps and constipation.

Constipation is a common adverse effect of clozapine (potentially affecting up to 60% of patients[1]) and complications relating to clozapine-induced gastrointestinal hypomotility (CIGH) e.g. paralytic ileus and bowel obstruction can be life-threatening unless managed appropriately. Reported fatality rates from CIGH, although very low, are many times the rates of those seen as a result of clozapine-induced blood dyscrasias.[2] 'Normal' bowel transit time in patients not prescribed clozapine has been reported to be around 23 hours. In patients prescribed clozapine, bowel transit times are over 4 times longer (median 104 hours).[1]

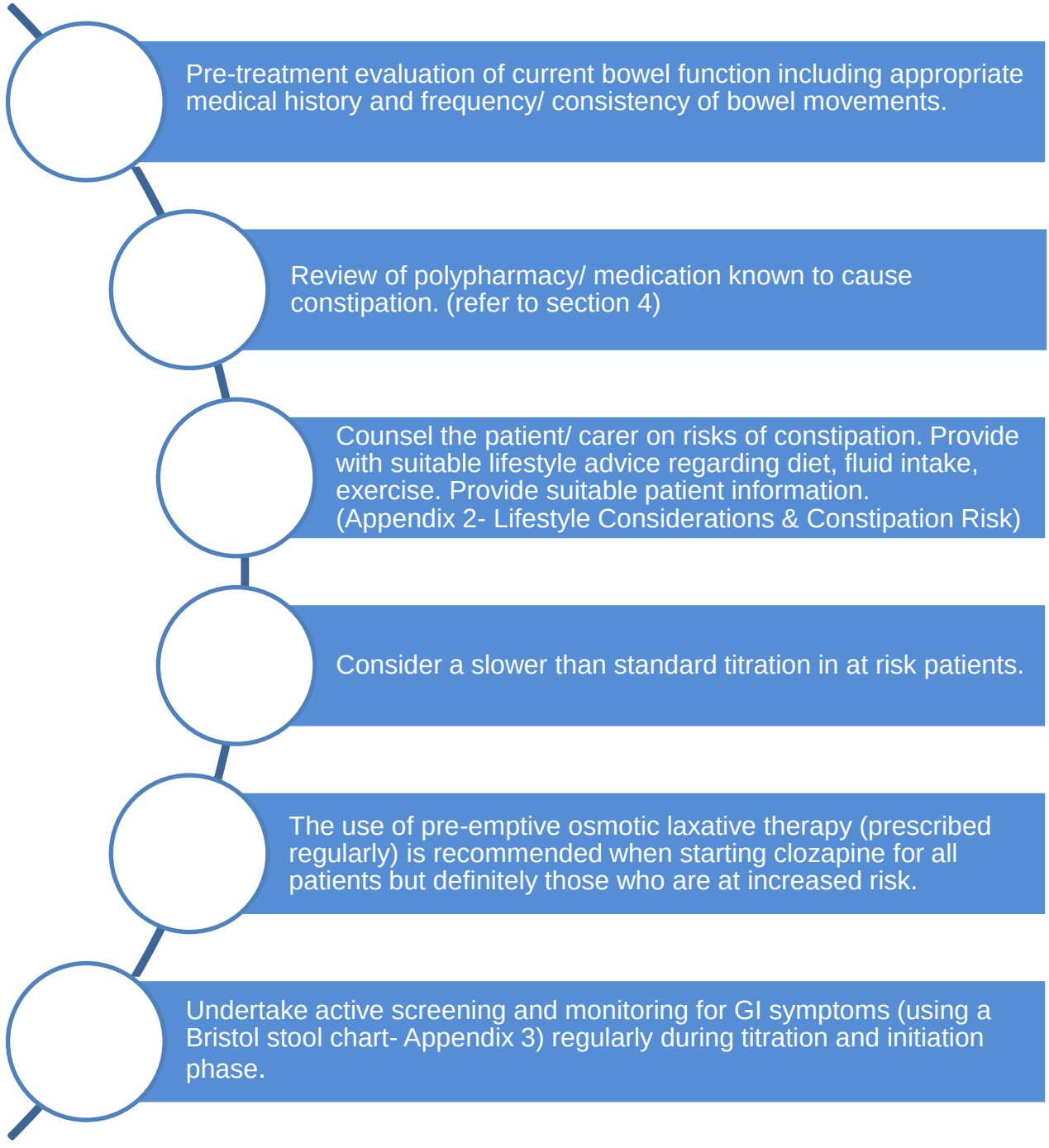
The risk of constipation with clozapine is associated primarily with its potent antimuscarinic effects, but antagonism of serotonergic and histaminergic receptors is also likely to be implicated.[3]

Antimuscarinic	→	Delayed bowel transit time
Antiserotonergic	→	Reduced bowel nociception (detection of painful stimuli)
Antihistaminergic	→	Increased risk of sedation

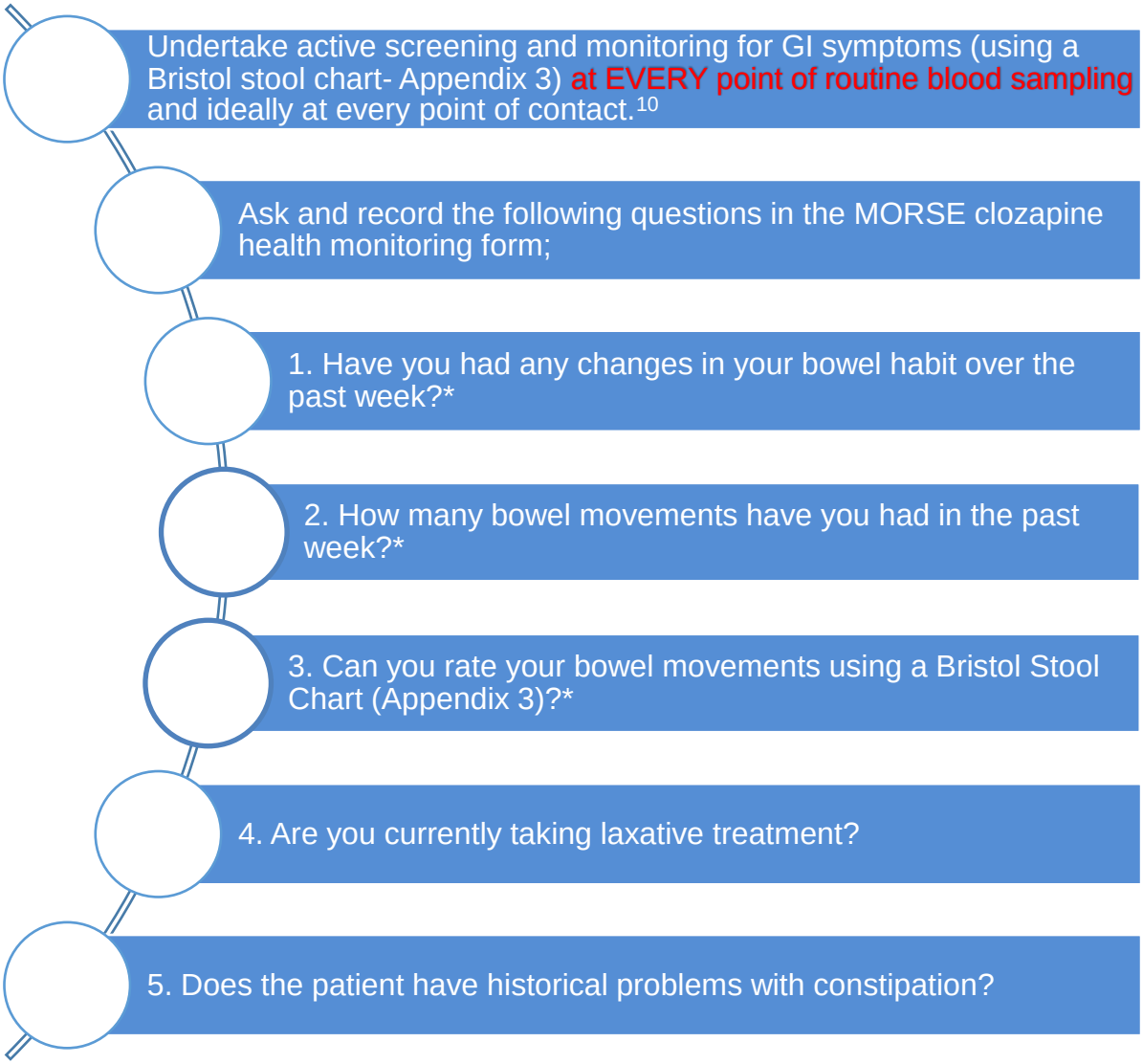
3. Risk factors for CIGH [4,5,6,7]	
Previous history of constipation/ GI disease/ lower abdominal surgery	Poor bowel habit
Obesity	Poor diet
Female sex	Increasing age esp. people over 60
Inactivity and low levels of exercise	Learning disabilities
Not prescribed laxative therapy	Concomitant medication known to cause constipation e.g. antimuscarinic medication, opiate analgesia
Clozapine recently initiated (highest risk in 1st 4 months of treatment)	High clozapine dose/ plasma levels (consider impact of interacting medications or stopping smoking on plasma levels)
Chronic illness associated with increased constipation risk e.g. hypothyroidism, Parkinson's disease, multiple sclerosis, diabetes mellitus)	Intercurrent illness e.g. infection (cytokines released during infection can inhibit clozapine metabolism and increase plasma levels)
Hospital inpatient stay	Dehydration

4. Medications associated with constipation *(not exhaustive- refer to BNF[8] and eMC[9])*	
Analgesics	opiate analgesia including compound analgesia e.g. co-codamol
Antimuscarinics	procyclidine, hyoscine; trihexyphenidyl; oxybutynin; tolterodine; solifenacin
Psychotropics	tricyclic antidepressants e.g. amitriptyline; antipsychotics e.g. chlorpromazine
Diuretics	furosemide; bendroflumethiazide
Metal ions	aluminium in antacids; iron salts

5. Workup pre- clozapine and initial titration



6. Monitoring for clozapine-induced constipation



* Patients (or their carers) should be encouraged to keep a note of bowel movements (day, time of stool, amount and Bristol Stool Chart number for each movement).

If there are any significant changes in bowel habit, abdominal pain or reports of having less than three bowel movements per week, this should prompt a medical assessment including an abdominal examination.

A change/ escalation in laxative treatment may be required.

Any patient with a high clozapine plasma level should be assessed for evidence of constipation.

7. Managing clozapine-induced constipation

Clozapine-induced constipation identified

- Recommend changes in lifestyle, diet, fluid intake.
- Consider a reduction in clozapine dose.
- Stop or decrease medication that can cause constipation.

If intestinal obstruction is excluded

- Commence an osmotic laxative (if not already prescribed) e.g. **Macrogols 1-3 sachets daily or lactulose 10-15ml twice daily**
- Add a stimulant laxative e.g. **senna 2 tabs at night.**
- Consider **docusate** (with softening and stimulating action).
- *Refer to section 10 for properties of treatment incl. time for effect.*
- Combinations of laxatives are often required.

Failure to relieve constipation wihin 48 hours

- Review current laxative treatment e.g. increase dose of laxative, add additional agent with different mode of action, consider use of enemas or assess need for manual evacuation.
- Treatment may required to be escalated quickly.

If severe symptoms emerge (refer to section 8)

- **Stop clozapine and other antimuscarinic agents.**
- Refer for urgent medical treatment and assess for bowel obstruction.

8. Severe signs and symptoms of CIGH requiring urgent intervention

9. Risk factors for CIGH during an inpatient hospital admission

An inpatient hospital admission can introduce new/ recurring risks that may worsen CIGH. Individuals prescribed clozapine should be closely monitored during admission with laxative therapy escalated where appropriate. Inpatients on clozapine experiencing constipation should have a stool chart (Appendix 4) initiated and updated at least daily including actively recording absence of bowel movement.

10. Laxative treatment *(refer to BNF[8] and eMC[9] for full dosing information)*

Type of laxative	Examples	Role in managing CIGH [11]
Osmotic laxatives	lactulose macrogols	• Draws water into stool • Not rapid acting • Takes up to 72 hours of regular use to work • Is not particularly helpful if used on as required basis • **Requires adequate fluid intake** (2-3 litres daily) • Some people find it difficult to drink the prescribed volume of macrogols • Useful in combination with stimulant laxative for established constipation • Faecal impaction may require treatment with high dose macrogols [12]
Stimulant laxatives	senna bisacodyl	• Increases GI motility • Fast-acting (within around 6-10 hours) • Should be used in combination with osmotic or softening laxative in established constipation • Prolonged use has been linked to degenerative changes in colonic muscles and nerves, however, stimulant laxatives should not be withheld for patients with CIGH
Softening laxatives	docusate	• Useful in combination with stimulant laxative for established constipation • May be more palatable for individuals than osmotic laxatives
Bulking laxatives	ispaghula	• Generally not helpful in CIGH as they are not effective in slow-transit constipation • Contraindicated in obstruction
Suppositories	glycerol bisacodyl	• Both stimulant laxatives, glycerol may be effective in 30 mins [5] , bisacodyl may be effective in 15-60 mins[9]
Enemas	sodium citrate phosphate	• Both osmotic laxatives, may be effective in around 20 mins [9]
In the event that clozapine-induced constipation is refractory to combinations of conventional laxatives and treatment is ineffective, advice should be sought from specialist gastrointestinal services [12]		

11. Key issues for managing constipation in patients on clozapine

- The risk of a clozapine treatment break is far outweighed by the ongoing risk to physical health in the event of severe GI symptoms.
- Only when acute GI symptoms have sufficiently improved, should there be consideration to recommencing clozapine and prophylactic measures should be used to mitigate ongoing risks.
- In the event of a treatment break of > 48 hours, clozapine will need to be retitrated.
- A high clozapine level should prompt an assessment for CIGH, however constipation can present in the absence of a high clozapine level.
- A patient prescribed clozapine who is not on a laxative should prompt a review.
- Being prescribed a laxative is not the same as taking a laxative. Patients may not consume all/ any of the prescribed dose.
- There can often be genuine complaints of palatability with laxative therapy especially osmotic laxatives. A change in prescribed laxatives may be required.
- Patients can be fully concordant with combinations of laxative therapy and still be constipated.
- Laxative therapy should be escalated where there are additive risk factors e.g. a change in concurrent medication.
- There is little rationale in using more than one agent from each class.
- Be aware of potential for overflow 'diarrhoea' especially if a Bristol Stool Chart score of 7 has been preceded by severe constipation.
- Don't wait for the individual to complain. Reduced bowel nociception (detection of painful stimuli) associated with clozapine means that patients on clozapine may not experience constipation in the same way as those not on clozapine.
- Patients with pronounced negative symptoms of schizophrenia may present with apathy, blunting of affect, poverty of speech and may lack motivation to address concerns regarding physical health.
- Ensure relevant information and advice regarding risks of constipation and individual patient management are shared with relevant healthcare professionals across primary and secondary care.

12. References

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3. West S et al. Clozapine-induced gastrointestinal hypomotility: a potentially life threatening adverse event. A review of the literature. *Gen Hosp Psychiatry* 2017; 46: 32-37

4. Medicines and Healthcare Regulatory Agency (MHRA). Clozapine- reminder of potentially fatal risk of intestinal obstruction. Oct 2017 https://www.gov.uk/drug-safety-update/clozapine-reminder-of-potentially-fatal-risk-of-intestinal-obstruction-faecal-impaction-and-paralytic-ileus

5. Taylor D et al. The Maudsley Prescribing Guidelines in Psychiatry. Wiley Blackwell. 14th edition

6. Clozaril Connect. Clozapine and Constipation

7. ZTAS Zaponex Fact Sheet April 2017

8. British National Formulary https://www.medicinescomplete.com

9. Electronic Medicines Compendium https://www.medicines.org.uk/emc

10. NHS Scotland National Standard for Monitoring the Physical Health of people being treated with clozapine. Scottish Government. CMO 2017 https://www.sehd.scot.nhs.uk/cmo/CMO(2017)04.pdf

11. National Institute for Health and Care Excellence NICE. Clinical Knowledge Summaries (CKS) Constipation. Last revised Nov 2024 https://cks.nice.org.uk/topics/constipation/

12. Specialist Pharmacy Service (SPS). Managing constipation in people taking clozapine. Oct 2022 https://www.sps.nhs.uk/articles/managing-constipation-in-people-taking-clozapine/

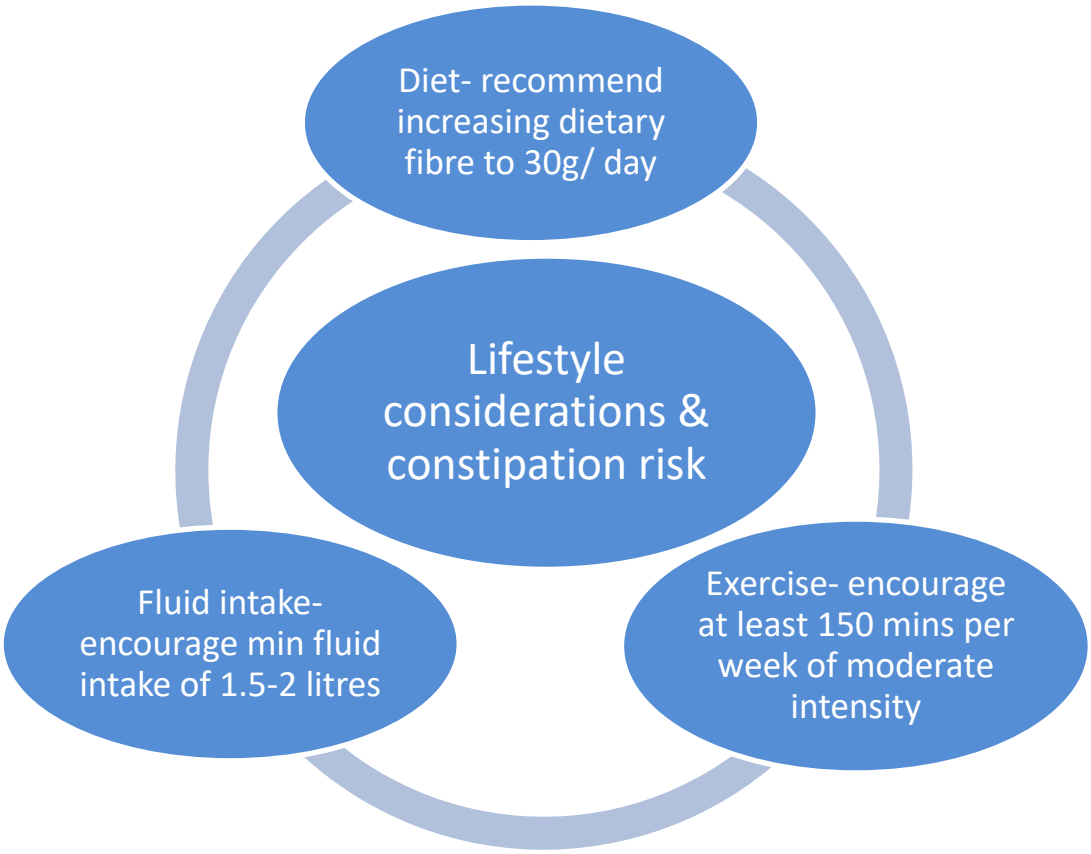
Appendix 1- Governance information for Guidance document

Lead Author(s):	Lorna Templeton
Endorsing Body:	ADTC
Version Number:	V2
Approval date	18th June 2025
Review Date:	1st June 2028
Responsible Person (if different from lead author)	

CONSULTATION AND DISTRIBUTION RECORD	
Contributing Author / Authors	Dr S. Cross, Consultant Psychiatrist MHLD pharmacy team
Consultation Process / Stakeholders:	MHLD Drug and Therapeutic Committee
Distribution	MHLD, OAMH and CAMHS medical, nursing and pharmacy staff, wards and community teams Acute medical, nursing and pharmacy staff Primary care NHSL clinical guideline website and app

CHANGE RECORD			
Date	**Lead Author**	**Change**	**Version**
April 22	L Templeton	*New guideline*	1
April 25	L Templeton	*Move to new CG template* *Update of section 6 in line with changes to changes to MORSE clozapine health monitoring form* *References updated* *Addition of lifestyle advice recommendations and* *NHS Lan sample stool chart in appendix*	2

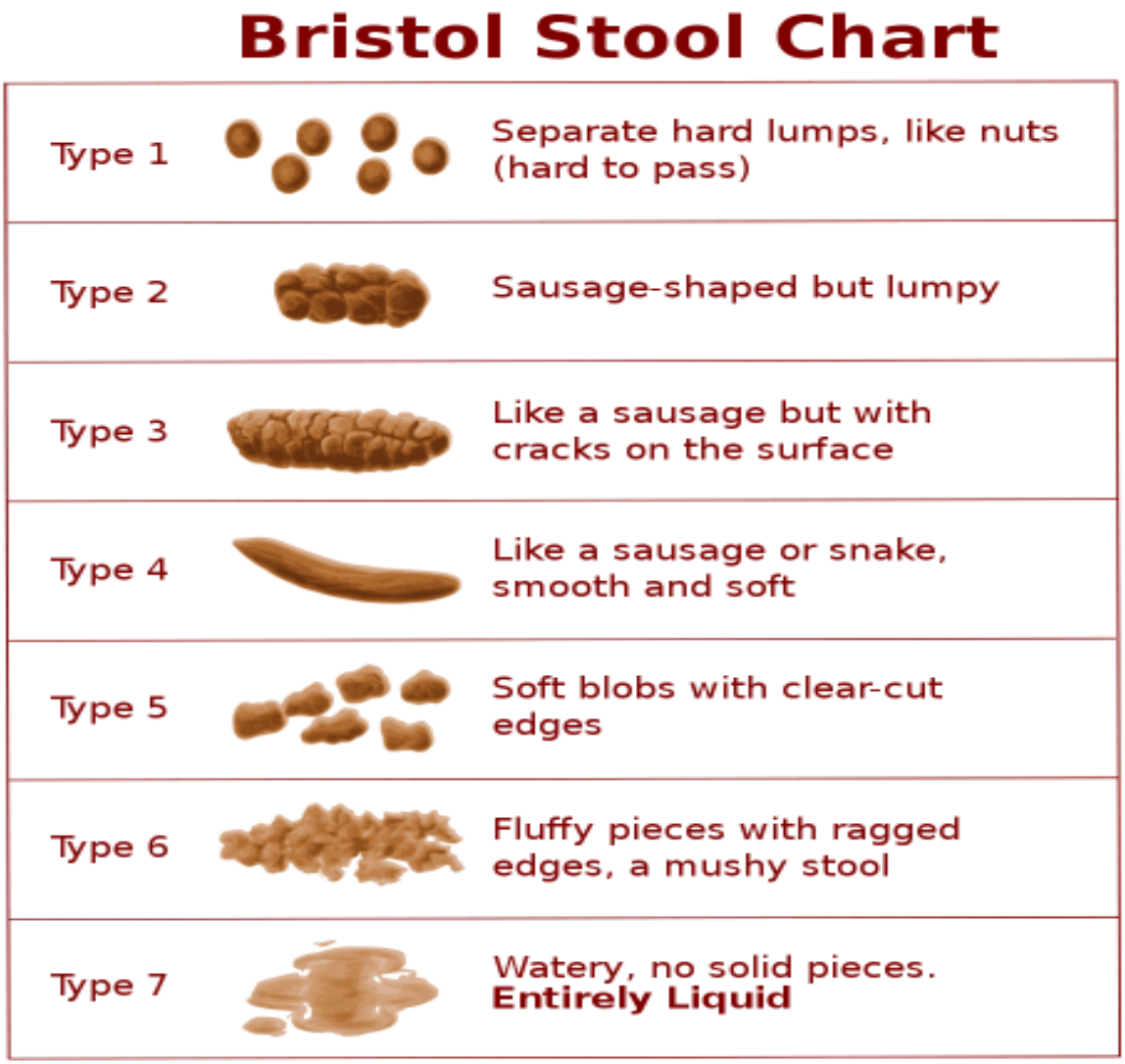
Appendix 2- Lifestyle Considerations & Constipation Risk



Choice and Medication- clozapine and constipation factsheet (patient info leaflet)

www.nhs.uk/live-well/eat-well/digestive-health/how-to-get-more-fibre-into-your-diet/

Appendix 3 – Bristol Stool Chart



Appendix 4 – NHS Lanarkshire Sample Stool Chart

CHI no ....
First name .... DOB ....../....../......
Last name .... Sex: ☐M ☐F
Address ....
....
....
or attach addressograph label here

University Hospital: ☐ Hairmyres ☐ Monklands ☐ Wishaw
Other hospital: (specify) ....
Ward: ....

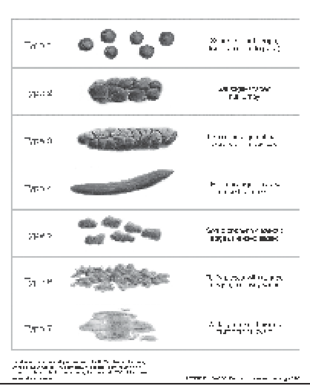
NHS Lanarkshire

Stool Chart (incorporating Bristol Stool Form Scale)

Date of onset: .... /........ /........
Time of onset: .... : .... (24 hour)

Presenting symptoms:

The Bristol Stool Form Scale



SAMPLE

Date	Time	Amount	Colour	Consistency (see Stool Scale)	Integrity of skin area buttocks/sacrum	Specimen sent to Microbiology	Print/Sign/ Designation

SAMPLE

LAT0010

NMAHPSTOCHA.23_098031

Stool Chart | Acute Care Services | NHSL | Page 1 of 2

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