

Advice for the Management of Clozapine-Induced Gastrointestinal Hypomotility (CIGH)

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Governance or Assurance Committee	Mental Health and Learning Disabilities Clinical Governance Group
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Contents		Page no.
1	Consultation and Distribution record	3
2	Change Record	3
3	Aim	3
4	Scope	3
5	Background	4
6	Risk factors for CIGH	4
7	Workup pre-clozapine and initial titration	5
8	Medications associated with constipation	5
9	Monitoring for clozapine-induced constipation	6
10	Managing clozapine-induced constipation	7
11	Severe signs and symptoms of CIGH requiring urgent intervention	7
12	Laxative treatment	8
13	Risk factors that may exacerbate CIGH during an inpatient hospital admission	9
14	Key issues for managing constipation in patients on clozapine	9
15	References	10
	Appendix – Bristol Stool Chart	10

1. Consultation and distribution

Contributing Author/ Authors	<ul style="list-style-type: none"> • MHL D Drug and Therapeutics Committee members
Consultation Process/ Stakeholders	<ul style="list-style-type: none"> • Psychiatry • MHL D nursing • MHL D pharmacy
Distribution	<ul style="list-style-type: none"> • Dissemination to all MHL D, OAMH and CAMHS medical, nursing and pharmacy staff, wards and community teams • Dissemination to acute medical, nursing and pharmacy staff • NHSL clinical guideline website and app • Medicines Matters and/or MHL D D&T newsletter

2. Change Record

Date	Author	Change	Version No.
Jan 22	Lorna Templeton	New Guideline	1.0

3. 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.




4. Scope

This guidance applies to all staff involved in the prescribing, administration and supply of clozapine in NHS Lanarkshire. It is the responsibility of senior managers to ensure that this guidance is implemented.

5. Background

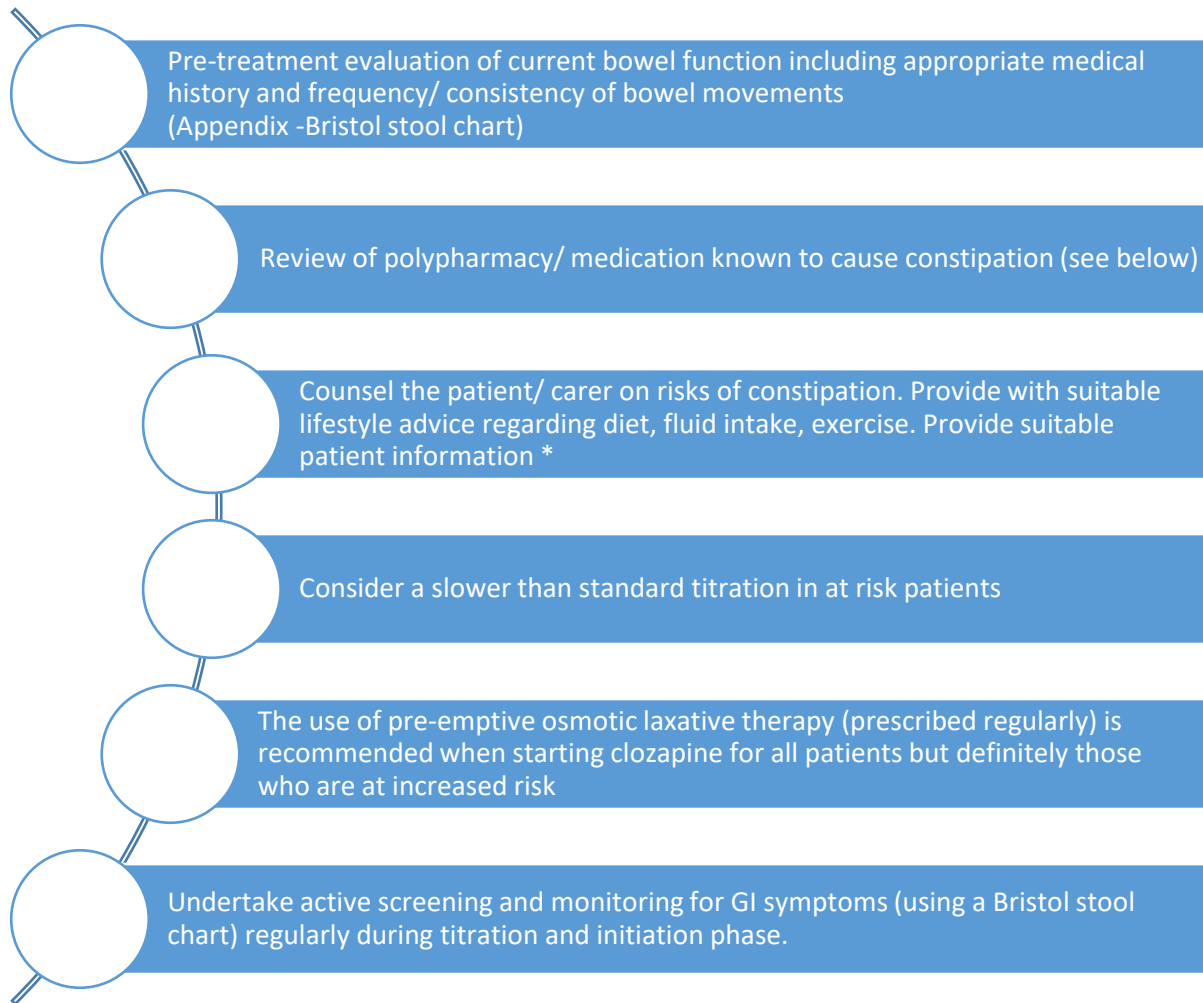
Constipation is a common adverse effect of clozapine and clozapine-induced gastrointestinal hypomotility (CIGH) can be life-threatening unless managed appropriately. Reported fatality rates from CIGH, although very low, are many times the rates of those seen as a result of clozapine-induced blood dyscrasias.¹ It has been suggested that 80% of patients prescribed clozapine exhibit GI hypomotility or ‘slow gut’ which may result in severe constipation, ileus and bowel obstruction. ‘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).²

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

6. Risk factors for CIGH ^{4,5,6,7}	
<ul style="list-style-type: none"> • Previous history of constipation/ GI disease/ lower abdominal surgery 	<ul style="list-style-type: none"> • Poor bowel habit
<ul style="list-style-type: none"> • Obesity 	<ul style="list-style-type: none"> • Poor diet
<ul style="list-style-type: none"> • Female sex 	<ul style="list-style-type: none"> • Increasing age esp. people over 60
<ul style="list-style-type: none"> • Inactivity and low levels of exercise 	<ul style="list-style-type: none"> • Learning disabilities
<ul style="list-style-type: none"> • Not prescribed laxative therapy 	<ul style="list-style-type: none"> • Concomitant medication known to cause constipation e.g. antimuscarinic medication, opiate analgesia
<ul style="list-style-type: none"> • Clozapine recently initiated (highest risk in 1st 4 months of treatment) 	<ul style="list-style-type: none"> • High clozapine dose/ plasma levels (consider impact of interacting medications or stopping smoking on plasma levels)
<ul style="list-style-type: none"> • Chronic illness associated with increased constipation risk e.g. hypothyroidism, Parkinson’s disease, multiple sclerosis, diabetes mellitus) 	<ul style="list-style-type: none"> • Intercurrent illness e.g. infection (cytokines released during infection can inhibit clozapine metabolism and increase plasma levels)
<ul style="list-style-type: none"> • Hospital inpatient stay 	<ul style="list-style-type: none"> • Dehydration

7. Workup pre- clozapine and initial titration

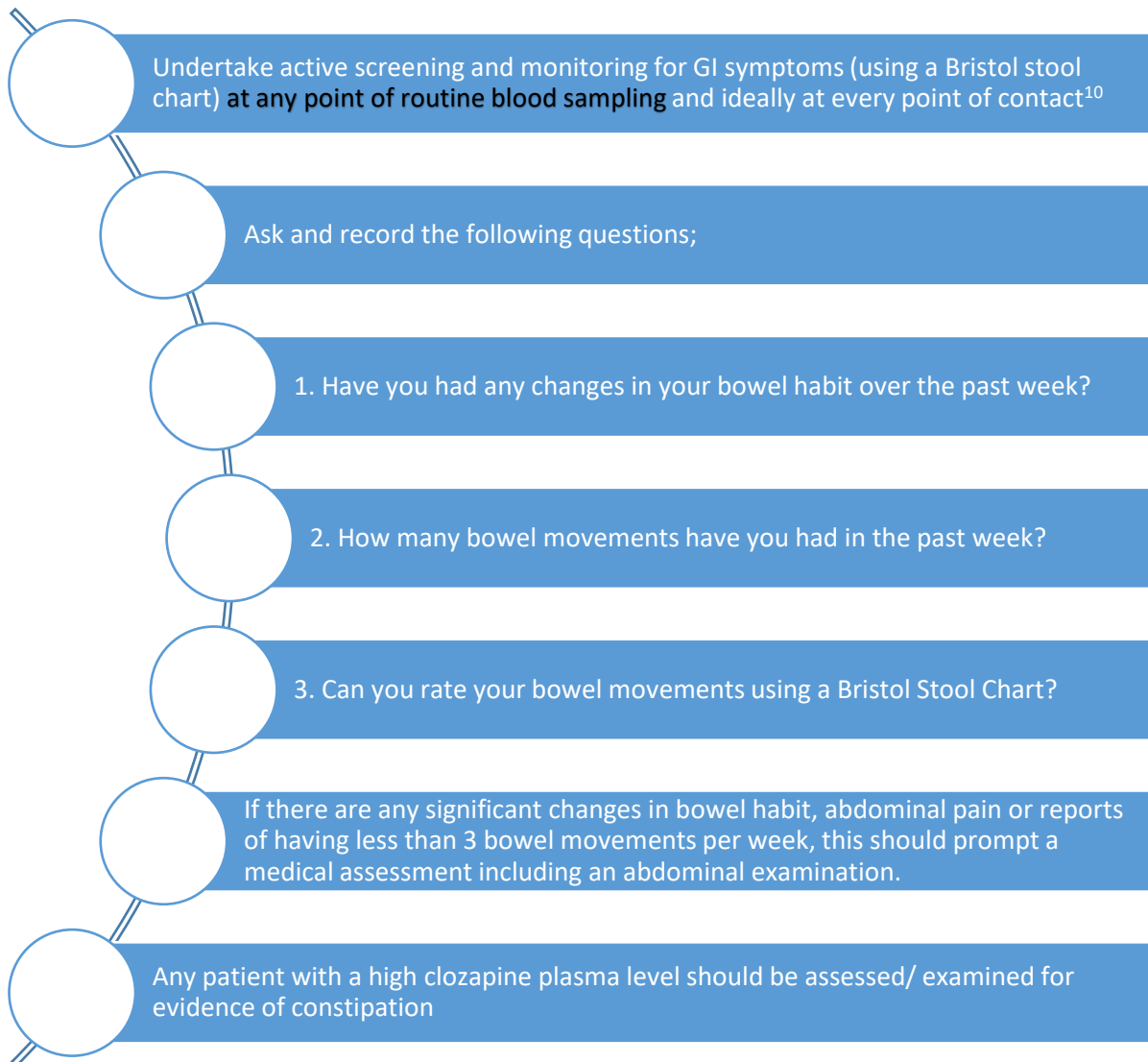


*[Choice and Medication- clozapine and constipation factsheet](#)

8. Medications associated with constipation (not exhaustive- refer to BNF⁸ and eMC⁹)

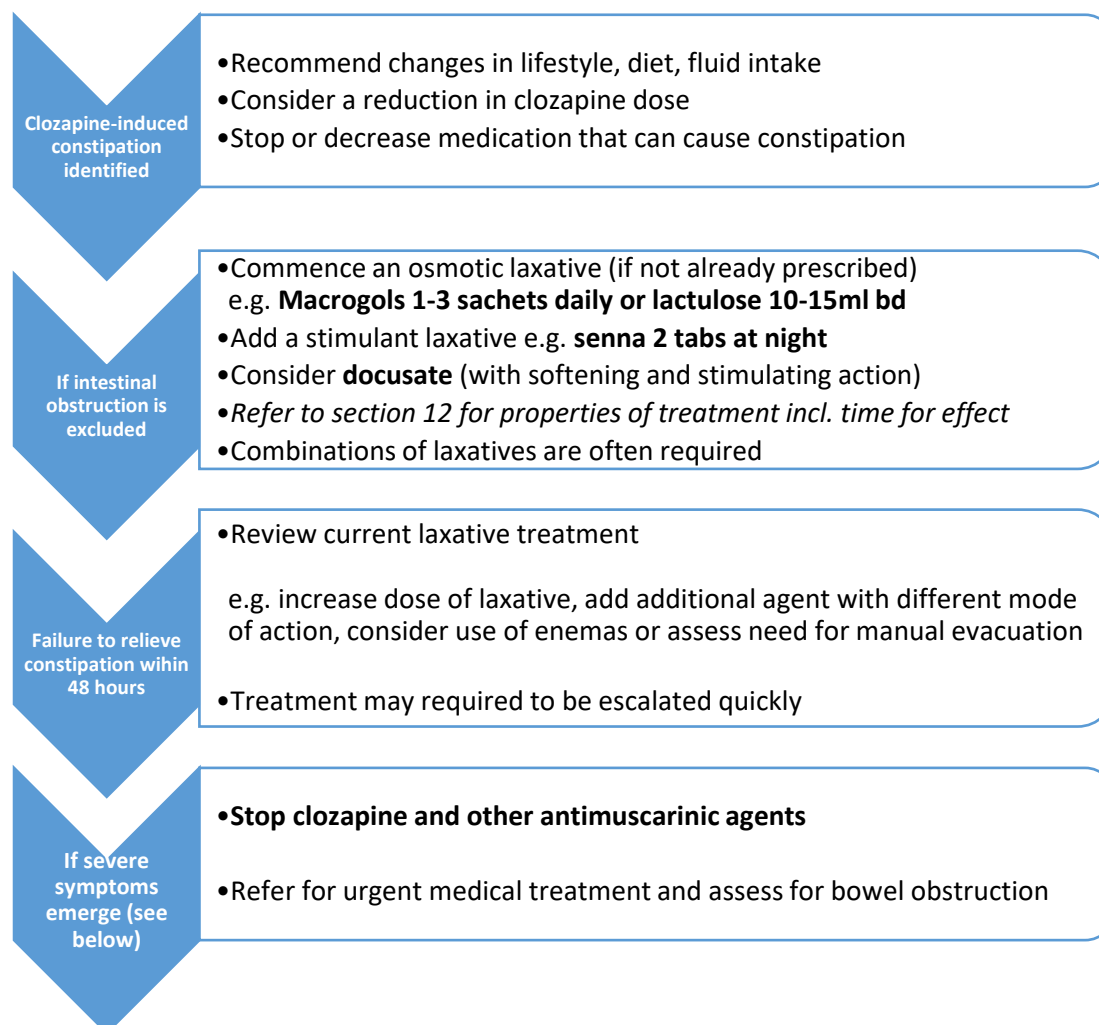
Analgesics	opiate analgesia including compound analgesia e.g. co-codamol
Antimuscarinics	hyoscine; trihexyphenidyl; oxybutynin; tolterodine; solifenacin
Psychotropics	tricyclic antidepressants e.g. amitriptyline; antipsychotics e.g. chlorpromazine
Diuretics	furosemide; bendroflumethiazide
Metal ions	aluminium in antacids; iron salts

9. Monitoring for clozapine-induced constipation



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10. Managing clozapine-induced constipation



11. Severe signs and symptoms of CIGH requiring urgent intervention



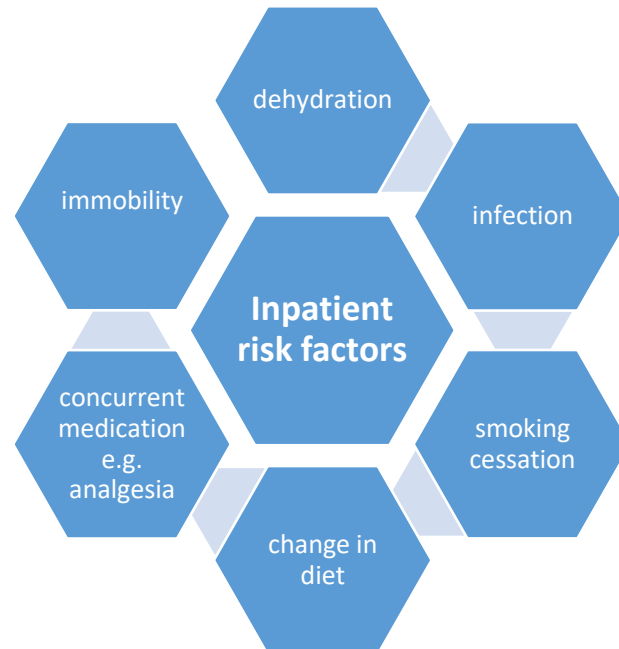
12. Laxative treatment (refer to BNF⁸ and eMC⁹ for full dosing information)

Type of laxative	Examples	Role in managing CIGH ¹¹
Osmotic laxatives	lactulose macrogols	<ul style="list-style-type: none"> • 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
Stimulant laxatives	senna bisacodyl	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Useful in combination with stimulant laxative for established constipation • May be more palatable for individuals than osmotic laxatives
Bulking laxatives	psyllium ispaghula	<ul style="list-style-type: none"> • Generally not helpful in CIGH as they are not effective in slow-transit constipation • Contraindicated in obstruction
Suppositories	glycerol bisacodyl	<ul style="list-style-type: none"> • Both stimulant laxatives, glycerol may be effective in 30 mins ⁵, bisacodyl may be effective in 15-60 mins⁹
Enemas	sodium citrate phosphate	<ul style="list-style-type: none"> • 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

13. Risk factors that may exacerbate 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.



14. 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.
- 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.
- 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.
- 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.

15. References

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Appendix - Bristol Stool Chart

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid