

May 13, 2019

Constipation Management Protocol for Clozapine Treated Patients (or Others on Severely Constipating Medications)

Background: Clozapine treated patients are at significant risk for ileus primarily due to its potent anticholinergic properties.¹ **While the average colonic transit time (CTT) in adults is 24 hours, for clozapine treated patients not on laxatives the median CTT is over 4 times longer (110 hours).**² Even with use of maximal doses of each of the 3 common classes of laxatives (docusate; osmotic; stimulant) the median CTT remains elevated at 62 hours.² Below are evidenced based recommendations for managing this serious problem:

1. Nonpharmacological Interventions ³⁻⁵

a.	Encourage physical activity. Being sedentary promotes constipation. Daily moderate exercise, e.g. walking for 20 minutes, has shown the greatest benefit.
b.	Encourage adequate fluid intake. Dehydration increases water resorption from the bowel, thereby hardening stool further. This is especially important during hot summer months.
c.	Encourage intake of fruits and vegetables, as adequate dietary fiber promotes bowel regularity.
d.	Encourage patients to report any substantial changes in bowel habits, stool consistency or color, blood in the stool, or development of straining, incomplete evacuation, or hard stools.

2. Minimize Medication Related Causes of Constipation ⁶⁻¹¹

a.	Where feasible, minimize or discontinue anticholinergic medications, as they prolong transit time, promote drying of stool, and increase risks of constipation, fecal impaction, or bowel obstruction. This includes antiparkinsonians (e.g. benztropine, diphenhydramine, trihexyphenidyl), and nonpsychiatric medications (e.g. oxybutynin, tolterodine, darifenacin, solifenacin, trospium, glycopyrrolate). The use of anticholinergic agents with clozapine doubles the ileus risk.
b.	DO NOT USE bulk laxatives (psyllium). When slowed transit times are present they may add to constipation mass, risk of fecal impaction and bowel obstruction.
c.	Iron and opioids: If the patient is not iron deficient or suffering from iron-deficiency anemia, avoid use of iron supplements as they promote constipation. In those with anemia consider holding iron during the initial 4-6 weeks of clozapine titration, and then add back slowly with careful monitoring of bowel habits. Opioids as much as possible should be stopped prior to clozapine initiation as these agents are profoundly constipating.
d.	Other medications associated with constipation include antiepileptics, diuretics, calcium channel blockers, cholinolytics, and serotonin antagonists (e.g. antiemetics). The effects of these agents is not as great as for anticholinergics, iron or opioids, but removal or modifying medications where possible may lessen the severity of constipation.

3. PRN Recommended Bowel Regimen ¹²⁻¹⁴

Treatment Step	Treatment Intervention
Step 1	Applies to anyone with a constipation history or who is started on potentially constipating medications. Give docusate 250 mg BID at the beginning of treatment (e.g. when starting clozapine), with rescue PRN medication (e.g. magnesium citrate 150 ml or magnesium hydroxide 30 ml q two days PRN lack of bowel movement).

May 13, 2019

Step 2	If step 1 isn't adequate, then add one osmotic laxative, e.g. polyethylene glycol 17 gms qam or lactulose 30 ml BID. Polyethylene glycol 3350 (Miralax) is generally superior to lactulose. (Lactulose is reserved for the treatment of hyperammonemia.)
Step 3	If steps 1 and 2 aren't adequate to alleviate constipation, then add one stimulant laxative. Options include sennosides starting at 17.2 mg qhs (max 34.4 mg BID) or bisacodyl starting at 5 mg qhs (max 30 mg per day).
Step 4	If steps 1-3 fail to adequately control constipation, then add one secretagogue (see Table 1). If the secretory laxative is effective, it may be possible to taper off the stimulant laxative and then the osmotic laxative.

Table 1. Basic Info on Intestinal Secretagogues ¹⁵⁻²⁰

Name	Mechanism	Starting Dose	Max Dose	Comments
Lubiprostone (Amitiza®)	Prostaglandin E1 analog	8 mcg BID	24 mcg BID	Give with food and water. No drug interactions. (Adverse effects can include nausea, abdominal pain, distention, diarrhea, dehydration, and rectal bleeding.)
Linaclotide (Linzess®)	Guanylate cyclase-C agonist	145 mcg qD	290 mcg qD	Give > 30 min before 1st meal. No drug interactions. (Adverse effects can include diarrhea, dehydration, hypokalemia, and rectal bleeding.)
Plecanatide (Trulance®)	Guanylate cyclase-C agonist	3 mg qD	3 mg qD	No drug interactions. (Adverse effects can include diarrhea, dehydration, hypokalemia, and rectal bleeding.)
Prucalopride (Motegrity®)	5HT ₄ agonist	2 mg qD	2 mg qD	No drug interactions. (Adverse effects can include headache, abdominal pain, nausea, diarrhea, abdominal distention, dizziness. Monitor for worsening depressive symptoms or emergence of suicidal thoughts/behavior.)

All the secretory laxatives cost about \$400 per month of treatment.

References

- Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. *Schizophrenia Bulletin*. 2012;38:592-8.
- Every-Palmer S, Ellis PM, Nowitz M, et al. The Porirua Protocol in the treatment of clozapine-induced gastrointestinal hypomotility and constipation: a pre- and post-treatment study. *CNS Drugs*. 2017;31:75-85.
- Dreher ML. Whole Fruits and Fruit Fiber Emerging Health Effects. *Nutrients*. 2018;10.
- Prichard DO, Bharucha AE. Recent advances in understanding and managing chronic constipation. *F1000Res*. 2018;7.
- Rawla P, Sunkara T, Raj JP. Updated review of current pharmacological and non-pharmacological management of irritable bowel syndrome. *Life Sci*. 2018;212:176-81.
- Leppert W. The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. *Adv Ther*. 2010;27:714-30.
- Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 12th ed. West Sussex, UK: Wiley-Blackwell; 2015.
- Domagala-Rodacka R, Cibor D, Szczeklik K, et al. Gastrointestinal tract as a side-effect target of medications. *Przegl Lek*. 2016;73:652-8.
- Every-Palmer S, Newton-Howes G, Clarke MJ. Pharmacological treatment for antipsychotic-related constipation. *Cochrane Database Syst Rev*. 2017;1:CD011128.
- Chen HK, Hsieh CJ. Risk of gastrointestinal Hypomotility in schizophrenia and schizoaffective disorder treated with antipsychotics: A retrospective cohort study. *Schizophr Res*. 2018;195:237-44.

May 13, 2019

11. Every-Palmer S, Inns SJ, Grant E, et al. Effects of Clozapine on the Gut: Cross-Sectional Study of Delayed Gastric Emptying and Small and Large Intestinal Dysmotility. *CNS Drugs*. 2019;33:81-91.
12. Wald A. Constipation: pathophysiology and management. *Curr Opin Gastroenterol*. 2015;31:45-9.
13. Wald A. Constipation: advances in diagnosis and treatment. *Jama*. 2016;315:185-91.
14. Serra J, Mascort-Roca J, Marzo-Castillejo M, et al. Clinical practice guidelines for the management of constipation in adults. Part 1: Definition, aetiology and clinical manifestations. *Gastroenterol Hepatol*. 2017;40:132-41.
15. Li F, Fu T, Tong WD, et al. Lubiprostone Is Effective in the Treatment of Chronic Idiopathic Constipation and Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Mayo Clin Proc*. 2016;91:456-68.
16. Shah ED, Kim HM, Schoenfeld P. Efficacy and Tolerability of Guanylate Cyclase-C Agonists for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2018;113:329-38.
17. Islam BN, Sharman SK, Browning DD. Clinical utility of plecanatide in the treatment of chronic idiopathic constipation. *Int J Gen Med*. 2018;11:323-30.
18. Hayat M, Zia H, Nusrat S. Lubiprostone in the treatment of chronic idiopathic constipation: an update on health-related quality of life and patient-reported outcomes. *Patient Relat Outcome Meas*. 2019;10:43-7.
19. Thomas N, Jain N, Connally F, et al. Prucalopride in clozapine-induced constipation. *Aust N Z J Psychiatry*. 2018;4867418774413.
20. Bassotti G, Usai Satta P, Bellini M. Prucalopride for the treatment of constipation: a view from 2015 and beyond. *Expert Rev Gastroenterol Hepatol*. 2019;13:257-62.