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Fact Sheet: Management of Clozapine-related Constipation

Background: Clozapine-treated patients are at significant risk for ileus primarily due to its potent anticholinergic properties.[1] **While the average colonic transit time 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] Other anticholinergic medications, especially in cases of anticholinergic polypharmacy may produce adverse effects similar to clozapine.[3-5]

Below are evidence-based recommendations for managing clozapine and anticholinergic medication-induced constipation:

II. Nonpharmacological Interventions [6-9]

Encourage physical activity. Being sedentary promotes constipation. Daily moderate exercise, e.g. walking for 20 minutes, has shown the greatest benefit.
Encourage adequate fluid intake. Dehydration increases water resorption from the bowel, thereby hardening stool further. This is especially important during hot summer months.
Encourage intake of fruits and vegetables, as adequate dietary fiber promotes bowel regularity.
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. However, patient report of symptoms is often unreliable.

2. Minimize Medication Related Causes of Constipation [10-15]

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 non-psychiatric medications (e.g. oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and glycopyrrolate). The use of anticholinergic agents with clozapine doubles the ileus risk.
b.	**DO NOT USE bulk laxatives (psyllium or polycarbophil). When slowed colonic transit times are present, bulk laxatives may add to constipation problems, and increase risk of fecal impaction and bowel obstruction.**
c.	**Iron:** If the patient is non 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, methadone, or buprenorphine initiation, and then add back slowly with careful monitoring of bowel habits.
d.	**Opioids:** When feasible, opioids used to treat pain (e.g. hydrocodone, etc.) should be stopped prior to clozapine initiation as these agents are profoundly constipating. Patients treated with agonist medications for opioid use disorder (methadone, buprenorphine) should be continued on the dose that is effective in maintaining abstinence from illicit opioids. These patients require enhanced bowel monitoring when treated with clozapine or another anticholinergic medication.

e.	Other medications associated with constipation include antiepileptics, diuretics, calcium channel blockers, cholinolytics, and serotonin antagonists (e.g. antiemetics). The effects of these agents are not as great as for anticholinergics, iron or opioids, but removal or modifying medications where possible may lessen severity of constipation.

III. Treatment Protocol [16-19, 4]

Stepwise Treatment Intervention	
Step 1	**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.) (see first line agents quality of evidence below)
Step 2	If step 1 isn't adequate to alleviate constipation, then **add one** stimulant laxative. Options include bisacodyl starting at 5 mg qhs (max 30 mg per day) or sennosides starting at 17.2 mg qhs (max 34.4 mg BID). If the patient is taking an opioid, then skip to step 3. (see first line agents quality of evidence below)
Step 3	If steps 1-2 fail to adequately control constipation, the next step depends on the etiology of the constipation: **Clozapine Patients: Add one** secretagogue (see Table 1). If the secretory laxative is effective, it may be possible to taper off the stimulant laxative first and then osmotic laxative. **OIC Patients: Add one** peripherally acting mu opioid receptor antagonist (see Table 2). If the peripherally acting opioid antagonist is effective, it may be possible to taper off other laxatives.
Step 4	**OIC Patients:** If step 3 fails to diminish constipation entirely, **add one** secretagogue (see Table 1). If the secretagogue in combination with the peripherally acting opioid antagonist is effective, it may be possible to taper off other laxatives.

First-line agents for treating clozapine-induced constipation, dosing, and evidence.
ACG=American College of Gastroenterology. Adapted from Meyer and Stahl 2019

Drug	Mechanism of Action	Starting Dose	Max Dose	Comments
Polyethylene glycol 3350 (PEG-3350)	Osmotic laxative	17 g QD	17 g BID	- Strong ACG recommendation - High quality of evidence
Lactulose	Osmotic laxative	30 ml QD	30 mi BID	- Strong ACG recommendation - Low quality of evidence
Bisacodyl	Stimulant laxative	5 mg QHS	15 mg BID	- Strong ACG recommendation - Moderate quality of evidence
Sennosides	Stimulant laxative	8.6 mg QD	17.2 mg BID	- Absence of controlled data

Table 1. Basic Info on Intestinal Secretagogues* [20-25]

Drug	Mechanism	Starting Dose	Max Dose	Comments
Lubiprostone (Amitiza®)	Prostaglandin E1 analog	8 mcg BID	24 mcg BID	**Give with food and water.** Adverse effects can include nausea, abdominal pain, distention, diarrhea, dehydration, and rectal bleeding.
Linaclotide (Linzess®)	Guanylate cyclase- C agonist	145 mcg qD	290 mcg	**Give > 30 min before 1st meal.** Adverse effects can include diarrhea, dehydration, hypokalemia, and rectal bleeding.
Plecanatide (Trulance®)	Guanylate cyclase- C agonist	3 mg qD	3 mg qD	Adverse effects can include diarrhea, dehydration, hypokalemia, and rectal bleeding.
Prucalopride (Motegrity®)	$5HT^4$ agonist	2 mg qD	2 mg qD	Adverse effects can include headache, abdominal pain, nausea, diarrhea, abdominal distention, dizziness. Monitor for worsening depressive symptoms or emergence of suicidal thoughts/behavior.

*None of these agents exhibit any drug-drug interactions. The proprietary secretory laxatives cost about $400 per month of treatment; however, lubiprostone has become less expensive because it is generically available.

Table 2. Basic Info on Peripherally Acting MU Opioid Receptor Antagonists [19,26]**

Drug	Mechanism	Starting Dose	Max Dose	Comments
Naloxegol (Movantik®)	Peripherally acting mu opioid receptor antagonist	25 mg qD (12.5 mg qD if creat clearance < 60 ml/min)	25 mg qD	**Give at least one hour before 1st meal or 2 hours after meal.** Contraindicated in patients taking strong CYP 3A4 inhibitors (e.g. clarithromycin, ketoconazole) **Drug interactions:** Avoid use with strong CYP 34A inducers (e.g. phenytoin). Avoid use with moderate CYP P450 3A4 inhibitors (e.g. diltiazem, erythromycin, verapamil). If concurrent use cannot be avoided, reduce naloxegol dose to 12.5 mg daily.

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Drug	Mechanism	Starting Dose	Max Dose	Comments
Naidemedine (Symproic®)	Peripherally acting mu opioid receptor antagonist	0.2 mg qd	0.2 mg qD	**Give with or without food.** Avoid use in patients with severe hepatic impairment (Child-Pugh Class C) **Drug interactions:** Avoid use with strong CYP 3A4 inducers. Moderate or strong CYP 3A4 inhibitors and P-glycoprotein inhibitors may increase naidemedine exposure.

** Contraindicated in known or suspected GI obstruction. Avoid concomitant use with other opioid antagonists. Avoid concomitant use with other opioid antagonists. Adverse effects can include GI perforation, severe or persistent diarrhea, abdominal pain, and opioid withdrawal. Naldemedine and naloxegol cost about $400 per month of treatment. Methylnaltrexone, a third agent, was not listed here due to its cost of >$2000/month. Note that these medications do not effectively cross the blood-brain barrier and do not interfere with opioid agonists or partial agonists used for pain treatment or medication assisted treatment of opioid substance use disorder.

References

1. Nielsen, J. and Meyer, J. M. (2012). Risk factors for ileus in patients with schizophrenia. Schizophrenia Bulletin, 38, 592-598.
2. Every-Palmer, S., Ellis, P. M., Nowitz, M., et al. (2017). The Porirua Protocol in the treatment of clozapine-induced gastrointestinal hypomotility and constipation: a pre- and post-treatment study. CNS Drugs, 31, 75-85.
3. Kreek, M. J. (1973). Medical Safety and Side-Effects of Methadone in Tolerant Individuals. Jama-Journal of the American Medical Association, 223, 665-669.
4. Farmer, A. D., Drewes, A. M., Chiarioni, G., et al. (2019). Pathophysiology and management of opioid induced constipation: European expert consensus statement. United European Gastroenterology Journal, 7, 7-20.
5. Haber, P. S., Elsayed, M., Espinoza, D., et al. (2017). Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. Drug and Alcohol Dependence, 181, 132-139.
6. Dreher, M. L. (2018). Whole Fruits and Fruit Fiber Emerging Health Effects. Nutrients, 10.
7. Prichard, D. O. and Bharucha, A. E. (2018). Recent advances in understanding and managing chronic constipation. F1000Res, 7, F1000-Faculty.
8. Rawla, P., Sunkara, T. and Raj, J. P. (2018). Updated review of current pharmacological and nonpharmacological management of irritable bowel syndrome. Life Sci, 212, 176-181.
9. Every-Palmer, S., Inns, S. J. and Ellis, P. M. (2020). Constipation screening in people taking clozapine: A diagnostic accuracy study. Schizophrenia Research, 220, 179-186.
10. Leppert, W. (2010). The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. Adv Ther, 27, 714-730.
11. Taylor, D., Paton, C. and Kapur, S. (2015). The Maudsley Prescribing Guidelines in Psychiatry. 12th ed. West Sussex, UK, Wiley-Blackwell.
12. Domagala-Rodacka, R., Cibor, D., Szczeklik, K., et al. (2016). Gastrointestinal tract as a side-effect target of medications. Przegl Lek, 73, 652-658.
13. Every-Palmer, S., Newton-Howes, G. and Clarke, M. J. (2017). Pharmacological treatment for antipsychotic-related constipation. Cochrane Database Syst Rev, 1, Cd011128.
14. Chen, H. K. and Hsieh, C. J. (2018). Risk of gastrointestinal Hypomotility in schizophrenia and schizoaffective disorder treated with antipsychotics: A retrospective cohort study. Schizophr Res, 195, 237-244.
15. Every-Palmer, S., Inns, S. J., Grant, E., et al. (2019). Effects of Clozapine on the Gut: Cross-Sectional Study of Delayed Gastric Emptying and Small and Large Intestinal Dysmotility. CNS Drugs, 33, 81- 91.
16. Wald, A. (2015). Constipation: pathophysiology and management. Curr Opin Gastroenterol, 31, 45-49.
17. Wald, A. (2016). Constipation: advances in diagnosis and treatment. JAMA, 315, 185-191.
18. Serra, J., Mascort-Roca, J., Marzo-Castillejo, M., et al. (2017). Clinical practice guidelines for the management of constipation in adults. Part 1: Definition, aetiology and clinical manifestations. Gastroenterol Hepatol, 40, 132-141.
19. Nee, J., Zakari, M., Sugarman, M. A., et al. (2018). Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology, 16, 1569-+.
20. Li, F., Fu, T., Tong, W. D., et al. (2016). 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, 91, 456-468.
21. Islam, B. N., Sharman, S. K. and Browning, D. D. (2018). Clinical utility of plecanatide in the treatment of chronic idiopathic constipation. Int J Gen Med, 11, 323-330.
22. Shah, E. D., Kim, H. M. and Schoenfeld, P. (2018). 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, 113, 329-338.
23. Thomas, N., Jain, N., Connally, F., et al. (2018). Prucalopride in clozapine-induced constipation. Aust N Z J Psychiatry, 4867418774413.
24. Bassotti, G., Usai Satta, P. and Bellini, M. (2019). Prucalopride for the treatment of constipation: a view from 2015 and beyond. Expert Rev Gastroenterol Hepatol, 13, 257-262. 25. Hayat, M., Zia, H. and
25. Nusrat, S. (2019). Lubiprostone in the treatment of chronic idiopathic constipation: an update on health-related quality of life and patient-reported outcomes. Patient Relat Outcome Meas, 10, 43-47.
26. Pergolizzi, J. V., Christo, P. J., LeQuang, J. A., et al. (2020). The Use of Peripheral mu-Opioid Receptor
27. Antagonists (PAMORA) in the Management of Opioid-Induced Constipation: An Update on Their Efficacy and Safety. Drug Design Development and Therapy, 14, 1009-1025. 27. Fakheri RJ, Volpicelli
28. FM. Things We Do for No Reason: Prescribing Docusate for Constipation in Hospitalized Adults. J Hosp Med. 2019 Feb;14(2):110-113. Chang L et al. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. Gastroenterology. 2023 Jun;164(7):1086-1106
29. Meyer JM, Stahl SM (2019) The Clozapine Handbook. Cambridge Univ Press New York, NY