Aspiration Pneumonia and Life-Threatening Bowel Obstruction: Unexpected Complications of Clozapine.

Learning objectives:
After completion of the article, the reader will be able to:

1. Describe the general pathophysiology of sialorrhea, gastrointestinal hypomotility, and their associated risks with clozapine or other antipsychotic medication use.
2. Identify signs and symptoms of clozapine-induced sialorrhea and gastrointestinal hypomotility, and their specific complications of aspiration pneumonia and life-threatening bowel obstruction.
3. List general pharmacologic and non-pharmacologic approaches for managing sialorrhea and gastrointestinal hypomotility in an adult patient.
4. Describe the general published evidence base for various pharmacologic treatments for clozapine-induced sialorrhea and gastrointestinal hypomotility.

Type of activity: knowledge
Target audience: pharmacists, including pharmacy residents

Authors:
Steven W. Samuels, PharmD, BCPS
Transitions of Care Clinical Pharmacist | Whole Person Care
Los Angeles County Department of Health Services

Amy Liu, PharmD
Clinical Pharmacology and Therapeutics Postdoctoral Fellow
University of California, San Francisco

Richard Duong, PharmD, BCPP
Clinical Pharmacist
Los Angeles County Department of Health Services

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Introduction: Unexpected Complications from Clozapine Use
Clozapine is well-known to pharmacists as a second-generation antipsychotic medication which requires a Risk Evaluation and Mitigation Strategy (REMS) program and carries multiple boxed warnings as mandated by the U.S. Food and Drug Administration (FDA). These include cautions for severe neutropenia, cardiomyopathies and myocarditis, seizures, increased mortality in elderly patients with dementia-related psychosis, and other adverse cardiovascular and respiratory effects.[1] However, two often-overlooked complications of clozapine use are sialorrhea and gastrointestinal hypomotility. Despite the potential for each complication to lead to life-threatening aspiration pneumonia or bowel obstruction, respectively, there is a paucity of practice guidelines on their prevention or mitigation.[2,3]

Several studies have reported increased risk of morbidity and mortality related to aspiration pneumonia (mortality rate 30%) and paralytic ileus (mortality rate 12%) secondary to clozapine use when compared with severe neutropenia (mortality rate 2%) for which clinical monitoring parameters are clearly defined (Table 1).[4] For example, some studies show the risk of mortality due to clozapine-induced gastrointestinal hypomotility (CIGH) may be at least three-fold that of agranulocytosis.[5] While the Clozapine REMS Program for routine neutrophil monitoring has been in place since 2015,[6] the FDA has only recently addressed risks associated with CIGH by mandating prescribing information updates to all clozapine-containing medications.[7] One interesting case report described an edentulous patient on clozapine who initially reported hypersalivation and constipation, then later developed a recurrent sore throat, cough, lethargy, and fever. After multiple hospitalizations and X-rays, he was found to have developed both pneumonia and fecal impaction during his course of treatment.[8]

Here, we aim to describe the pathophysiology of clozapine-induced hypersalivation and gastrointestinal hypomotility, and how these adverse effects may lead to serious complications including aspiration pneumonia and bowel obstruction. In both acute and ambulatory care settings, early and proactive risk assessment, prevention, monitoring, and management of these potentially fatal clozapine adverse effects are key steps in reducing the need for acute clinical services and improving health outcomes.

Table 1: Clozapine Dosing and Therapeutic Drug Monitoring Basics[1,9,10]

Clozapine Dosing
• Initial dose for schizophrenia: 12.5 mg orally daily or twice daily • Titration: Increase by 25 to 50 mg daily as tolerated • Target dose: 300 to 450 mg daily in 2 to 3 divided doses by the end of 2 weeks • Dosing may be individualized to treatment response • Discontinuation should be gradual over a 1 to 2-week period
Clozapine Levels and Monitoring
• Therapeutic clozapine level: Guidelines recommend at least 350 ng/mL • Potential therapeutic range: 250 to 420 ng/mL • No clear upper safety threshold. Doses above 600 mg may correlate to adverse effects such as seizures, with an FDA maximum daily dose of 900 mg.
General Monitoring • Initially up to weekly complete blood cell count with differential and absolute neutrophil count, although may be less frequent during COVID-19 pandemic • See prescribing information for monitoring and REMS program requirements • Systematic inquiry and monitoring for sialorrhea and constipation
Clozapine Metabolites

Important Clozapine Active Metabolites
• Norclozapine (N-desmethylclozapine)
  ○ More activity
  ○ Longer half-life than parent compound clozapine
• Clozapine N-Oxide

Clozapine:Norclozapine Ratio • Drawing levels is not yet routine. May provide additional practical information especially if concern for drug interactions, adherence, or toxicity. • Low ratio <0.5 (more Norclozapine) suggests poor adherence in past 24 hours or rapid metabolism • High ratio >3 (more parent Clozapine) suggests metabolism inhibited or saturated
Clozapine Interactions and Other Considerations

• Clozapine is a substrate of CYP1A2, 2D6, and 3A4. Notable CYP1A2 interactions below.
• CYP1A2 Inducers
  ○ Cigarette smoking (8 cigarettes per day can decrease clozapine levels 50%)
  ○ Cannabis smoking
• CYP1A2 Inhibitors
  ○ Caffeine
  ○ Infection and inflammation (e.g. febrile illness)

Other Considerations • There is high individual variation in dose response • Decreased gastrointestinal transit time may increase clozapine absorption

Background: Hypersalivation

Hypersalivation is defined as an excessive production or flow of saliva, the fluid secreted from the salivary glands of the mouth. The most common medical term for this symptom is "sialorrhea", less-commonly referred to as "ptyalism". "Drooling" or "mouth-watering" are used colloquially to describe when saliva visibly outflows from the mouth after pooling in the oral cavity. This CE will use the medical term sialorrhea when referring to hypersalivation as a pathophysiologic symptom.[11]

Sialorrhea may occur when salivation is in excess of what is necessary or safe. The typical range of daily saliva production has been reported as 800-1500 mL, with a 95% reduction during sleep.[12] Sialorrhea is not necessarily an increased production of saliva and is not part of normal physiologic response, as with physical or psychological perception of a stimulus like food. For example, decreased physical capacity to keep saliva in the mouth or difficulty swallowing may occur secondary to neurological disorders such as Parkinson's disease, multiple sclerosis, or stroke.[13]

"Excessive salivation" is a common side effect of clozapine with an estimated incidence between 13% to 48%.[10] Several studies observed up to 80% incidence of clozapine-induced sialorrhea.[12] A dedicated clozapine treatment center found 92% prevalence of excessive salivation based on specific survey tools.[14] While clozapine-associated agranulocytosis poses risks of serious and fatal infections, clozapine-induced sialorrhea is a notable side effect that can reduce medication adherence and impact quality of life.[12]

The major salivary glands of the mouth, which are responsible for a majority of daily saliva production, include the parotid, submandibular, and sublingual glands. Minor salivary glands

are microscopic and present throughout the aerodigestive tract, including on or in the lips, tongue, cheeks, soft palate, nose, sinuses, and larynx.[15]

The parasympathetic system is primarily responsible for control of salivation via the M3 muscarinic receptor. However, the M3 receptor is paradoxically antagonized by clozapine and does not appear to play the primary role in clozapine-induced sialorrhea. Clozapine is an M1 (highest affinity), M2, and M5 muscarinic receptor antagonist as well as an M4 receptor agonist. Clozapine also binds alpha-adrenergic, dopamine, serotonin, and H1 histamine receptors. Clozapine-induced sialorrhea is hypothesized to occur through several pathways, including:[12,14,16,17]

- Direct M4 muscarinic agonism, thought to selectively increase salivation to a greater degree than the drug's M3 antagonistic effect which can decrease salivation;
- $Alpha_2$ adrenoreceptor antagonism, thought to ultimately increase blood flow to the salivary glands due to unopposed Beta-adrenoreceptor activity; and
- Decreased laryngeal peristalsis or inhibition of the swallowing reflex via various neurotransmitters. Notably, studies have shown no difference in the salivary flow itself for patients taking clozapine, making interference with swallowing the most likely working hypothesis.

Patients experiencing clozapine-induced sialorrhea may be recognized by various behaviors. It is important to identify these behaviors, along with signs and symptoms of sialorrhea, while managing a patient taking clozapine in both outpatient and inpatient settings. Patients and providers may not immediately attribute these symptoms to clozapine treatment. Patients experiencing clozapine-induced sialorrhea may:[12,18]

- Frequently wipe their mouth with a tissue or cloth or carry a "spit cup" or towel.
- Regularly swallow excess saliva, increasing chances of bloating, gas pain, or flatulence.
- Awaken from a choking sensation or a wet pillow, as sialorrhea is often more prevalent throughout the night.
- Have fatigue or somnolence due to nighttime awakenings.
- Have a hoarse-sounding voice or other vocal changes.
- Have an irritated perioral area or chin and be at greater risk of skin infection.
- Have damp or foul-smelling clothing.

An additional consideration for clozapine-induced sialorrhea includes a patient-centered approach to their experience of the adverse effect. Drooling in public may be socially stigmatizing and can negatively affect quality of life and treatment adherence. Sialorrhea may also be under-reported by patients due to lack of systematic inquiry by providers.[14]

Special Consideration: Aspiration Pneumonia and Pneumonitis

The human body has compensatory reflexes to sialorrhea, such as gagging and coughing. Both reflexes may become chronic.[13] If these reflexes are impaired (e.g. in neurologic disorders, sedation, decreased peristalsis, or severe debilitation), excess saliva may be aspirated, thereby increasing risks of serious complications such as pneumonia or asphyxiation.[12] Patients with

underlying psychiatric disorders may have a predisposition to clozapine-associated aspiration pneumonia given its multi-factorial nature.[18]

Patients taking clozapine who present to an emergency department, are in the ICU, or in another critical care setting may have a greater potential for pharmacist intervention. In a patient presenting with shortness of breath, hypoxia, cough, or other respiratory symptoms, clozapine-induced sialorrhea should be considered a contributing factor. Other symptoms of concern include difficulty swallowing, choking, or weight loss.[18] Management strategies in this CE, including setting-specific strategies like elevating the head of a hospital bed, can be considered to prevent serious outcomes.

Non-Pharmacologic Management of Clozapine-Induced Sialorrhea

There are several strategies to manage clozapine-induced sialorrhea without starting a novel medication, which may lead to a prescribing cascade. When possible, attempt non-pharmacologic management as first-line treatment (Table 2). In clinical practice, a common non-pharmacologic strategy recommended for excessive nighttime drooling is to place a towel over the patient's pillow.[19]

Prevention of sialorrhea is another strategy. One effective and simple non-pharmacologic method that may be attempted first is to increase swallowing frequency by chewing sugar-free gum. Further strategies that may decrease the risk of this adverse effect include titrating clozapine doses slowly, dose reduction, and therapeutic drug monitoring of clozapine plasma levels (Table 1). Augmentation with other antipsychotic medications to maintain efficacy can also be considered, although most current guidelines recommend against antipsychotic polypharmacy unless otherwise indicated.[20] Furthermore, as the relationship between clozapine dose and clozapine-induced sialorrhea remains unclear, clinical judgment should be used to determine if a dose reduction is appropriate.

Table 2: Non-Pharmacologic Management Strategies for Clozapine-Induced Sialorrhea[12,13,19]

Strategy	Considerations
Educate on side effect possibility	May alleviate fear, shame, or stigma
Increase swallowing frequency, e.g. by chewing sugar-free gum	Directly decreases drooling. Gum prompts swallowing, appears socially acceptable.
Limit sugary foods	Decreases salivation
Swallow multiple times without inhalation and while squeezing nostrils	May decrease choking sensation
Watch for skin breakdown on the lips and around the chin	Patient self-monitoring to prevent infection
Elevate hospital bed or head with multiple pillows at bedtime	May decrease nighttime choking
Place towel over pillows	In mild nocturnal sialorrhea, prevents soaking and sleep disruption

Lay on side (lateral decubitus position)	For profuse sialorrhea, decreases risk of aspiration
Wear a specialized “chin cup” device	For patients unable to care for themselves, has been used in children and elderly

Consultation with speech therapists, who are trained to assess aspiration risk and coach patients on head positioning, lip and mouth exercises, and frequent swallowing, can be considered.[13] Other providers may perform a barium swallow study to assess risk and rule out other disease processes. Radiation of salivary glands can be performed if a patient is refractory to medical and surgical interventions, such as removal of the salivary glands.[21]

Pharmacologic Management of Clozapine-Induced Sialorrhea

If conservative treatment strategies prove ineffective in managing clozapine-induced sialorrhea, pharmacologic oral and topical agents may be considered (Table 3). Current literature favors the use of anticholinergic agents (i.e. muscarinic receptor antagonists) with limited systemic side effects, such as sublingual ipratropium bromide spray. Other muscarinic receptor antagonist agents include benztropine, glycopyrrolate, and scopolamine. Generally, the lowest effective dose for the individual should be used. A range of doses have been studied for safety and efficacy of these agents.[22]

Of note, use of anticholinergic agents may be limited in patients with narrow-angle glaucoma, bladder obstruction, prostatic hypertrophy, gastrointestinal motility disorders, or who are elderly. For these individuals, an alpha$_2$-adrenergic agonist may be a viable alternative, given the role of the parasympathetic autonomic nervous system in salivation control. Side effects of alpha$_2$-adrenergic agonists, such as hypotension, urinary retention, constipation, or bradycardia, may raise tolerability and safety concerns. Therefore, close monitoring and alternative treatment strategies should be considered.

With respect to the treatment of sialorrhea secondary to Parkinson’s disease, several randomized controlled trials showed a reduction of saliva production with botulinum toxin injected into the parotid gland. Clinical application of this discovery led to favorable outcomes, as in a case-study by Kahl et al. Investigators achieved a distinct reduction in clozapine-induced sialorrhea following bilateral parotid gland injection with botulinum toxin A (150 International Units) in a male patient with schizophrenia receiving clozapine 600 mg per day and unresponsive to a trial of atropine.[19] As with alpha$_2$-adrenergic agonists, most of the current evidence regarding the clinical use of botulinum toxin for clozapine-induced sialorrhea is limited.

Table 3 summarizes practical pharmacologic treatment options for clozapine-induced sialorrhea. This table excludes options that are not available in the United States, are not commonly used in practice, or are supported only by case reports or case series in the literature. There is no strong evidence available for most pharmacologic treatments of clozapine-induced sialorrhea beyond only a few small trials.

Table 3: Pharmacologic Management Strategies for Clozapine-Induced Sialorrhea[12,19]

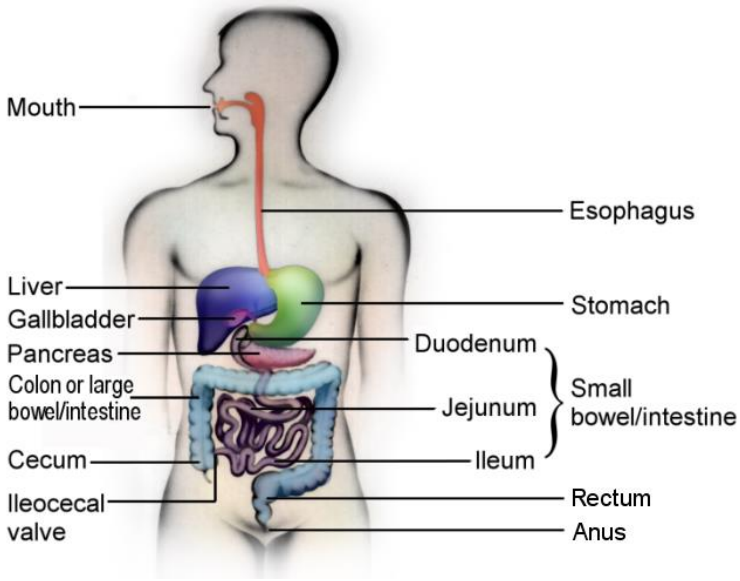
Drug	Dosing	Clinical Pearls
Muscarinic receptor antagonists		
Ipratropium bromide nasal spray 0.03-0.06% (Atrovent)	1-2 sprays sublingually at bedtime	Low systemic absorption.
Atropine 1% eye drops (Isopto Atropine)	3-4 drops sublingually at bedtime and up to three times daily as needed	Monitor for rebound effect in the morning or upon discontinuation due to short half-life.
Benztropine (Cogentin)	1-2 mg orally twice daily	Consider combination with terazosin 2 mg orally daily with close blood pressure monitoring. Systemic anticholinergic effects may contribute to gastrointestinal hypomotility and constipation.
Glycopyrrolate (Robinul)	1 mg orally twice daily or 2-4 mg orally at bedtime	Slow, erratic absorption. Evidence from other indications such as perioperative sialorrhea.
Scopolamine (Transderm Scop)	1.5 mg topical patch applied behind the ear every 72 hours	Patch use may increase adherence or be considered for severe sialorrhea.
Trihexyphenidyl (Artane)	5-15 mg orally at bedtime	Limited evidence.
Alpha$_2$-adrenergic agonists		
Clonidine (Catapres-TTS, Catapres)	0.1-0.2 mg topical patch applied weekly or 50-100 mcg orally at bedtime	Patch takes 3-4 days to reach steady state plasma concentrations. Monitor blood pressure. May increase sedation, and rarely exacerbate depression or psychosis. Patient may develop tolerance.
Botulinum toxin A injection (Botox) Procedurally injected into parotid salivary glands. Consider last-line for refractory or severe clozapine-induced sialorrhea, especially in the setting of neurological disease. Monitor for dental caries and periodontal infections.		

Background: Gastrointestinal Hypomotility

Clozapine-induced gastrointestinal hypomotility (CIGH) has been described throughout the literature. The estimated incidence of "constipation" as a clozapine side effect is between 14% to 25%. However, constipation is also grouped under "abnormal digestive peristalsis" and listed alongside "gastrointestinal hypomotility", "ischemic bowel disease", and "paralytic ileus" among other complications.[10] Studies have cited up to 60% incidence of CIGH.[23]

After mechanical and enzymatic breakdown in the mouth and swallowing of food down the esophagus, the gastrointestinal tract (Figure 1) propels the resulting "bolus" via mechanisms of peristalsis and regulation of sphincter tone. Gastrointestinal motility, or generally the movements of the digestive system, can be impacted by a variety of disorders affecting the nerves and muscles involved in these mechanisms. Examples of disruptions to gastrointestinal motility include gastroesophageal reflux disease, delayed gastric emptying (gastroparesis), irritable bowel syndrome, and aging.

Figure 1: Overview of the Gastrointestinal Tract[24]



Take-Home Message
1. Pharmacists can detect and provide management strategies for constipation as a symptom of clozapine-induced gastrointestinal hypomotility (CIGH). 2. Pharmacists should query patients about constipation as part of a clozapine-specific or general antipsychotic drug therapy evaluation. 3. Early and accurate detection of constipation can translate to prevention of undesired outcomes, such as acute care utilization or decreased medication adherence.

In contrast to clozapine's effects on salivation via agonism of muscarinic M4 receptors, gastrointestinal hypomotility is attributed to clozapine antagonism of other muscarinic receptors and activity on serotonergic receptors.[25–27] M3 muscarinic receptors expressed in the digestive tract stimulate intestinal smooth muscle contractility and digestive enzyme secretion when activated.[28] As stated above, clozapine specifically antagonizes the M1, M2, M3, and M5 receptors. Antagonism of the H1 receptor and its associated sedation may also play a role.[26] Finally, clozapine-induced hypersalivation itself may lead to dehydration and increase the risk of constipation, as can other side effects such as inactivity due to sedation.[29]

In practice, a patient's complaint of constipation to a psychiatrist or other specialist provider may not prompt consideration as an antipsychotic-induced side effect. Constipation may be perceived as a common discomfort that can be managed by a primary care provider. However,

a pharmacist should be prompted to query the patient about constipation as part of a clozapine-specific or general antipsychotic drug therapy evaluation. A pharmacist can effectively detect and provide management strategies for constipation as a symptom of gastrointestinal hypomotility. Even in less serious cases of constipation, early and accurate detection can translate to prevention of undesired outcomes, such as acute care utilization or decreased medication adherence.

Special Consideration: Paralytic Ileus, Esophageal Dysmotility, and Other Serious Adverse Effects

Multiple fatalities have been described in the literature as a result of severe complications of CIGH.[25,26] Although outside the scope of this CE to describe each complication, pharmacists should recognize the following risks when gastrointestinal motility is decreased: fecal impaction, colon perforation, megacolon, paralytic ileus, esophageal dysmotility, peritonitis, gastric outlet obstruction, bowel ischemia, aspiration pneumonia due to inhalation of feculent vomitus, and sepsis.

A government bulletin in New Zealand noted ten reports of death from clozapine-associated constipation, paralytic ileus, and esophageal dysmotility, while only one death was reported from clozapine-associated agranulocytosis through the national monitoring program in 2007. The authors attributed this difference to routine continuous monitoring of neutrophil counts, in contrast to lack of systematic monitoring for constipation. Pharmacists should be aware of clozapine's potential to affect motility throughout the entire GI tract and that CIGH may have a higher mortality rate than agranulocytosis.[23,27]

A study using a Danish registry examined risk factors for paralytic ileus. The authors found clozapine use for schizophrenia was associated with a two-fold increased risk of ileus overall and a 6-fold increase in paralytic ileus resulting in death. The study also noted that total length of treatment and higher doses were associated with these adverse effects, with an average of 3 years elapsing from time of first clozapine prescribing to time of ileus.[26] Another review found risk factors for CIGH to be "older age, male gender, patients in the first four months of treatment, co-prescription of constipating agents, higher daily dose of clozapine, and previous CIGH".[2] Length of treatment and gender as risk factors are particularly conflicting in the literature.[30,31]

Non-pharmacologic Management of Clozapine-induced Gastrointestinal Hypomotility

Non-pharmacologic approaches for managing gastrointestinal hypomotility are generally consistent with counseling for prevention and treatment of constipation. Possible strategies are summarized below in Table 4, with special consideration given to patients with schizophrenia or who are managed with clozapine.

Clinical considerations for preventing severe complications of CIGH were discussed in a case report of bowel infarction and included:[25]

- Consider deprescribing or avoiding use of concomitant medications with anticholinergic properties (e.g. opioids, benztropine or medications for extrapyramidal symptoms, tricyclic antidepressants, oxybutynin or medications for urinary incontinence).
- Smoking induces Cytochrome P450 1A2 (CYP1A2), which is involved in the metabolism of clozapine. Therefore, patients who quit or decrease smoking may have an increased susceptibility to clozapine's adverse effects.
- Patients experiencing constipation may present with nonspecific symptoms of CIGH complications, including abdominal pain or a distended abdomen.

Table 4: Non-Pharmacologic Management Strategies for Clozapine-Induced Gastrointestinal Hypomotility[10,26,32]

Strategy	Considerations
Increase dietary fiber	Patients with schizophrenia may have decreased fiber intake.
Increase exercise and physical activity	Patients with schizophrenia may have more sedentary lifestyles secondary to their negative symptoms or sedating medications.
Ensure adequate hydration	Consider concomitant disease states such as heart failure or cirrhosis that may have fluid restrictions. Consider fluid intake from ingestion of powdered laxative medications.
Counsel to pay attention to body cues (e.g. constipation) as a warning sign for more severe problems	Patients with schizophrenia may have decreased pain sensitivity and awareness of somatic symptoms.
Monitor bowel movements	Consider asking about and documenting frequency and consistency
Consider physical exam and documentation of bowel sounds when applicable	Patients may not report symptoms.
Conduct motility studies (e.g. performed with radiopaque markers or wireless capsules)	For concerning cases requiring evaluation or confirmation, or in the setting of a study

Pharmacologic Management of Clozapine-induced Gastrointestinal Hypomotility

A Cochrane review published in 2017 attempted to address pharmacologic management of antipsychotic-induced constipation. However, the authors identified few studies, with poor quality data, and which were very likely to be biased. The authors themselves stated "the results were disappointing" and studies did not compare common pharmacological interventions, such as polyethylene glycol or stool softeners. The studies included in this review compared mannitol to rhubarb soda and phenolphthalein, and glycerol suppositories to massage and acupuncture.[33]

Since then, little has changed in terms of specific evidence in the setting of treating clozapine or antipsychotic-induced constipation. Clinical practice should be guided by general constipation

management guidelines and principles, with a focus on prevention. One study found that asking about constipation symptoms as part of a clinical exam had a sensitivity of only 18% for diagnosing CIGH. The investigators included a case-study of a nurse taking clozapine who had no noticeable symptoms of CIGH despite no bowel movements for 15 days. Thus, the authors recommended prophylactic pharmacotherapy for clozapine-associated constipation, similar to co-prescribing for a patient starting opioids.[32] Others have similarly advocated for a low threshold to starting prophylactic laxatives in patients on clozapine.[29] A daily regimen of polyethylene glycol powder or docusate can be considered first, based on patient preference of formulation and are commonly-available pharmacologic options. Patients can subsequently decrease use of prophylactic constipation medications if diarrhea occurs or hold for loose stools.

Table 5 is a summary of common medications used for constipation, adapted in part from Clozapine in Practice: A Toolkit published by the College of Psychiatric and Neurologic Pharmacists (CPNP).[34] Of note, psyllium husk and other bulking agents should be avoided in the setting of gastrointestinal hypomotility as these agents may increase the risk of bowel perforation.[34]

Table 5: Selected Pharmacologic Options for Clozapine-Induced Gastrointestinal Hypomotility

Drug	Dosing	Clinical Pearls
Osmotic Laxatives		
Polyethylene glycol 3350 (Miralax)	17 grams (using measuring capful) orally daily to TID	Low systemic absorption. **Consider as first-line.** Powder, may encourage fluid intake.
Lactulose (Enulose)	10-40 grams orally daily	Powder or liquid. Most commonly used as liquid e.g. in hepatic encephalopathy treatment. Sweet taste may not be preferred for some patients.
Magnesium hydroxide (Milk of Magnesia)	400-1200 mg orally four times daily	Most commonly liquid. May be more effective for acute constipation rather than chronic use. Consider various flavorings. Consider renal function given magnesium content.
Stimulant Laxatives		
Bisacodyl (Dulcolax)	5-15 mg orally daily	**Consider as second-line vs. sennosides +/- docusate.**
Sennosides (Senna, Senokot)	17.2 mg (two tablets) orally daily, may titrate up to four tablets	**Consider as second-line vs. bisacodyl.** Consider combination with docusate especially in setting of opioid-induced constipation.
Stool Softeners		

Docusate sodium (Colace)	100-500 mg orally daily or in divided doses	Consider in combination with sennosides especially in setting of opioid-induced constipation.
Other Agents – limited evidence, costly, or consider in severe/refractory cases.		
Lubiprostone (Amitiza)	24 mcg orally daily, titrate to two times daily	Costly. Limited evidence, based on a case report.
Orlistat (Alli, Xenical)	120 mg orally three times daily	May not be tolerable due to gastrointestinal side effects. Limited evidence, one RCT showing efficacy.
Linaclotide (Linzess)	72-145 mcg orally daily	Given 30 minutes prior to first meal. Capsule may be opened and beads dissolved in room-temperature water or applesauce.
Pyridostigmine (Mestinon)	10 mg orally twice daily to 60 mg orally three times daily	Consider in recurrent severe cases.

Potential Algorithm for Prevention of Clozapine-Induced Gastrointestinal Hypomotility

While there is a paucity of guidelines for risk evaluation and mitigation of CIGH, practitioners can utilize patient-centered strategies to reduce needs for acute care and hospitalization. CPNP's Clozapine in Practice: A Toolkit,[34] CCHCS/DHCS Care Guide for Clozapine,[35] and a screening and treatment algorithm proposed by West et al.[2] offer starting points for synthesizing a potential algorithm that can be customized to various care settings. Table 6 summarizes key strategies from these practice guides into a potential treatment algorithm. During treatment initiation and established clozapine therapy, three goals include:

- Prevent acute constipation, ileus, and life-threatening bowel obstruction
- Minimize polypharmacy in constipation management
- Maintain normal bowel function

Table 6: Proposed Clozapine-Induced Gastrointestinal Hypomotility Treatment Algorithm*

GOAL: Prevent acute constipation, ileus, and life-threatening bowel obstruction

Screen for CONSTIPATION RISK
• May be performed by dispensing or direct patient care pharmacist
• Possible Tools:
  ○ Norgine Risk Assessment Tool for Constipation[36]
  ○ Constipation Risk Assessment Scale[37]
  ○ Glasgow Antipsychotic Side-effects Scale for Clozapine[38]
• Document comorbid medical conditions, laboratory tests to exclude treatable causes of constipation (e.g. hypothyroidism)

Assess risk factors for SEVERE COMPLICATIONS of CIGH

- Higher doses of clozapine and/or clozapine serum levels (Table 1)
- Concomitant anticholinergic agents and opioids
- Inhibition of Cytochrome P450 1A2 (e.g. caffeine use, febrile illness)
- History of frequent constipation or bowel obstruction

RED FLAGS prompting referral to acute care

- Increased duration between or absent bowel movements
- Moderate to severe abdominal discomfort, pain, cramping
- Diarrhea or vomiting
- Metabolic acidosis
- Hemodynamic instability
- Paralytic ileus or intestinal obstruction

GOAL: Minimize polypharmacy in constipation management

Comprehensive MEDICATION REVIEW

- Agents that may contribute to constipation or slowing intestinal transit (examples):
  - Anticholinergic: antihistamines, anticonvulsants, antispasmodics, urinary incontinence agents, antidepressants (e.g. tricyclics, paroxetine)
  - Beta blockers: atenolol
  - Calcium channel blockers: verapamil, diltiazem, nifedipine
  - Cation-containing agents: iron, aluminum, calcium
  - NSAIDs: ibuprofen, naproxen
  - Opioids

GOAL: Maintain normal bowel function

COUNSEL all patients

- Regular monitoring of bowel function
  - At least weekly during first 4 months (initiation phase)
  - At least during every mental health provider visit (maintenance phase)
- Establish history and baseline bowel patterns

PROPHYLACTIC BOWEL REGIMEN

- Patient-by-patient basis
- Consider low threshold to initiate regimen if significant risk factors present
- Assess risks and benefits of CIGH prophylaxis
  - Patient's ability to reliably report symptoms
  - Barriers of increasing medication burden

CHRONIC treatment of constipation	ACUTE treatment of constipation
• Maximize first drug, then augment with second agent • First-line: Polyethylene glycol 3350 or lactulose • Second-line: Bisacodyl or sennosides +/- docusate sodium	• Magnesium hydroxide or magnesium citrate • Glycerin suppository • Sodium phosphate enema

AVOID psyllium husk and other bulking agents
These agents may increase the risk of bowel perforation.[33]

*Adapted from three clozapine care guides.[2,34,35]

Conclusion

Clozapine is an effective and long-standing atypical antipsychotic medication for treatment-refractory schizophrenia. Clozapine-induced sialorrhea and gastrointestinal hypomotility are lesser-known adverse drug reactions with potentially serious, even fatal, complications. In 2020, the FDA strengthened its requirements for updating prescribing information for all clozapine products. A new warning was added to include risks of untreated constipation leading to serious bowel problems.[7] Several non-pharmacologic and pharmacologic approaches to management of clozapine-induced sialorrhea and gastrointestinal hypomotility focus on prevention and treatment of these side effects to reduce the need for acute care or emergency services. The strategies highlighted in this CE may aid pharmacists in ensuring the safe and effective use of clozapine.

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