

MHC clozapine toolbox

Robin Hieber, PharmD, BCPP¹

¹Assistant Professor of Pharmacy Practice, Northwestern University Chicago College of Pharmacy

KEYWORDS

clozapine, monitoring

The toolbox beginning on the next page was compiled to provide several documents that will assist you with treating your clozapine patients. It includes a suggested protocol for initiating someone on clozapine (see Figure 1). We have also included guidelines for CBC monitoring (see Table 1), at initiation and beyond, as well as monitoring recommendations for when an interruption in treatment occurs (see Figure 2). Since constipation is a major adverse event associated with the use of clozapine, attached you will find an overview of both prevention and treatment of constipation compiled by Beth Hall at Fulton State Hospital in Missouri (see Figure 3). Another side effect that often afflicts a person taking clozapine is hypersalivation. Here, we have a table which outlines options to minimize one's sialorrhea (see Table 2). Or read this Current Psychiatry [clinical pearl](#) which discusses pharmacologic treatments for hypersalivation. We hope that these documents are helpful with regard to a patient's clozapine treatment.

REFERENCES

1. Clozapine Initial Titration Protocol" adapted from the Center for Behavioral Medicine's form.
2. CBC monitoring from Clozaril Package insert, Novartis. Last revised, December 2010.
3. Sockalingam S, Shammi C, Remington G. Clozapine-induced hypersalivation: a review of treatment strategies. *Can J Psychiatry*. 2007;52(6):377-84. PubMed PMID: [17696024](#).
4. Liang CS, Ho PS, Shen LJ, Lee WK, Yang FW, Chiang KT. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. *Schizophr Res*. 2010;119(1-3):138-44. DOI: [10.1016/j.schres.2010.02.1060](#). PubMed PMID: [20299191](#).
5. Sharma A, Ramaswamy S, Dahl E, Dewan V. Intraoral application of atropine sulfate ophthalmic solution for clozapine-induced sialorrhea. *Ann Pharmacother*. 2004;38(9):1538. DOI: [10.1345/aph.1E077](#). PubMed PMID: [15252196](#).
6. Lamba G, Ellison JM. Reducing clozapine-induced hypersalivation. *Current Psychiatry*. 2011;10(10):77-8. Available from: <http://www.currentpsychiatry.com/topics/schizophrenia-other-psychotic-disorders/article/reducing-clozapine-induced-hypersalivation/51165ce6e0614bo25604d59e483eca7a.html>

How to cite this editor-reviewed article

Hieber R. MHC clozapine toolbox. *Ment Health Clin* [Internet]. 2011;1(5):82-91. Available from: <http://dx.doi.org/10.9740/mhc.n87735>

Figure 1. PHYSICIAN'S ORDERS FOR CLOZAPINE INITIAL TITRATION PROTOCOL

DRUG ALLERGIES

UNIT _____

ORDERED DATE/TIME	NOTE: Check for history of and/or current constipation before initiating Clozapine		INDICATION /RATIONALE
	Initiate Clozapine po as follows:		For Refractory Psychosis
	† For a MALE patient	† For a FEMALE patient	
	DAY	DIRECTIONS	
	1.	25 mg HS	
	2.	25 mg AM & 25 mg HS	
	3.	25 mg AM & 25 mg PM & 25 mg HS	
	4.	25 mg AM & 25 mg PM & 50 mg HS	
	5.	25 mg AM & 50 mg PM & 50 mg HS	
	6.	50 mg AM & 50 mg PM & 50 mg HS	
	7.	50 mg AM & 50 mg PM & 100mg HS	
	8.	50 mg AM & 50 mg PM & 100mg HS	
	9.	50 mg AM & 100 mg PM & 100mg HS	
	10.	100 mg AM & 200 mg HS	
	11.	100 mg AM & 200 mg HS	
	12.	100 mg AM & 250 mg HS	
	13.	100mg Q AM & 300mg HS & continue dose	
<input type="checkbox"/>	EKG (check box on left to order EKG)		Risk of myocarditis
<input type="checkbox"/>	Obtain Clozapine level with third weekly CBC		Therapeutic Monitoring
<input checked="" type="checkbox"/>	Weekly CBC with differential		Possible agranulocytosis; monitor WBC & ANC
<input checked="" type="checkbox"/>	Docusate sodium 100 mg PO BID		To prevent constipation
<input checked="" type="checkbox"/>	High fiber diet		
<input type="checkbox"/>	Other: _____		
<input checked="" type="checkbox"/>	Discontinue & refrain from using any benzodiazepines during titration (may resume benzodiazepines after clozapine dosage is stable).		To avoid respiratory depression
<input checked="" type="checkbox"/>	Monitor for signs of myocarditis i.e. unexplained fatigue, dyspnea, tachypnea, chest pain, palpitations, fever or other signs of heart failure. Benign tachycardia is common with clozapine (i.e. 25%), but may also be sign of myocarditis.		Black Box warning
<input checked="" type="checkbox"/>	Pulse & blood pressure (lying & standing) 30 minutes before & after each dose of clozapine x 2 weeks; then resume routine vital signs.		Risk of tachycardia, hypotension and hypertension
<input checked="" type="checkbox"/>	When each blood pressure is taken ask patient if he/she has experienced dizziness or has fallen since last dose of clozapine. Inform physician if patient answers yes to either question.		Risk of hypotension
<input checked="" type="checkbox"/>	Assess & document BMs. Inform physician if no stool reports x 2 days. Please instruct patient on ways to manage constipation (i.e. increase intake of fluids, fruit, vegetables & cereals with high fiber content; and exercise).		Possible constipation

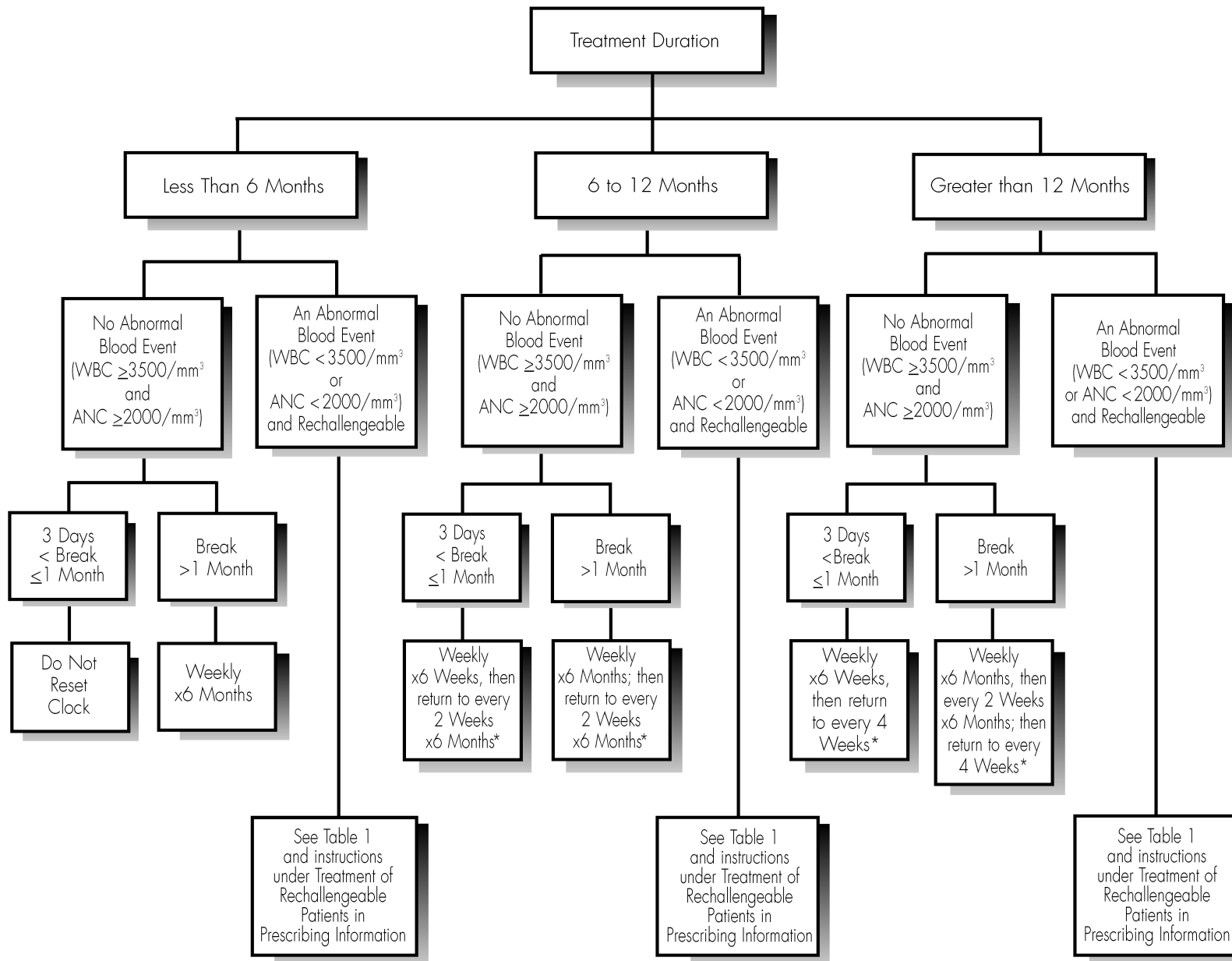
Physician's signature: _____ Date: _____ Time: _____

Table 1. Frequency of monitoring based on stage of therapy or results from WBC count and ANC monitoring tests

SITUATION	HEMATOLOGICAL VALUES FOR MONITORING	FREQUENCY OF WBC AND ANC MONITORING
Initiation of therapy	WBC $\geq 3500/\text{mm}^3$ ANC $\geq 2000/\text{mm}^3$ *	Weekly for 6 months
6 months – 12 months of therapy	All results for WBC $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$	Every 2 weeks for 6 months
12 months of therapy Immature forms present	All results for WBC $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$ N/A	Every 4 weeks indefinitely Repeat WBC and ANC
Discontinuation of therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of WBC $\geq 3000/\text{mm}^3$ or ANC $\geq 1500/\text{mm}^3$	1. Repeat WBC and ANC 2. If repeat values are $3000/\text{mm}^3 \leq \text{WBC} \leq 3500/\text{mm}^3$ and $\text{ANC} > 2000/\text{mm}^3$, then monitor twice weekly
Mild leukopenia Mild granulocytopenia	$3500/\text{mm}^3 > \text{WBC} \geq 3000/\text{mm}^3$ and/or $2000/\text{mm}^3 > \text{ANC} \geq 1500/\text{mm}^3$	Twice weekly until WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$ then return to previous monitoring frequency
Moderate leukopenia Moderate granulocytopenia	$3000/\text{mm}^3 > \text{WBC} \geq 2000/\text{mm}^3$ and/or $1500/\text{mm}^3 > \text{ANC} \geq 1000/\text{mm}^3$	1. Interrupt therapy 2. Daily until WBC $> 3000/\text{mm}^3$ and ANC $> 1500/\text{mm}^3$ 3. Twice weekly until WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$ 4. May rechallenge when WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe leukopenia Severe granulocytopenia	WBC $< 2000/\text{mm}^3$ and/or ANC $< 1000/\text{mm}^3$	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC $> 3000/\text{mm}^3$ and ANC $> 1500/\text{mm}^3$ • Twice weekly until WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$ • Weekly after WBC $> 3500/\text{mm}^3$
Agranulocytosis	ANC $\leq 500/\text{mm}^3$	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC $> 3000/\text{mm}^3$ and ANC $> 1500/\text{mm}^3$ • Twice weekly until WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$ • Weekly after WBC $> 3500/\text{mm}^3$

*Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) clozapine-induced agranulocytosis or granulocytopenia.

Figure 2. TRACKING PATIENTS: RESUMING MONITORING FREQUENCY AFTER INTERRUPTION IN THERAPY



*Transitions to reduce frequency of monitoring only permitted if all WBC ≥3500 and ANC ≥2000.

Figure 3. Pharmacy Constipation Protocol, Mar 2011

Beth Hall, PharmD, BCPP

In this stepwise approach, we treat increasing levels of severity of constipation. It is a guideline, not a rule in how to approach constipation. The steps should be *approached* sequentially, but the physician does not need to follow them in order. This method provides a rubric to approach constipation pharmacologically, while minimizing potential risks due to medication.

EVERYONE

- Lifestyle Modifications:
 - Increase exercise
 - Increase dietary fiber (Prune Juice, Prunes)
 - Increase hydration status (if necessary)

STEP-WISE APPROACH

- **Step 1**
 - Fiber 2 scoops PO BID
 - Docusate 100mg BID
 - PRN MOM 30mL QD
- **Step 2**
 - Lactulose 15mL BID
 - Docusate 100mg BID
 - PRN MOM 30mL QD
- **Step 3**
 - Lactulose 30mL BID
 - Docusate 200mg BID
 - PRN MOM 30mL QD
- **Step 4**
 - Lactulose 45mL BID
 - Docusate 200mg BID
 - PRN MOM 30mL QD
- **Step 5**
 - Lactulose 45mL BID
 - Docusate 200mg BID
 - Bisacodyl 10mg BID
 - PRN MOM 30mL QD
- **Step 6**
 - Polyethylene Glycol 17g PO BID
 - Docusate 200mg BID
 - Bisacodyl 20mg BID
 - MOM 30mL QD
- **Step 7**
 - Evacuation Protocol
 - GI Consult Necessary

AVAILABLE AGENTS

<u>Drug</u>	<u>Unit</u>
Benefiber	1 Scoop
Bisacodyl	5mg Tab
Metamucil	1 Packet
Docusate	100mg Cap
Lactulose	15 mL
Mag Citrate	1 Bottle
Milk of Mag	30 mL
Mineral Oil	15 mL
PEG 3350	17g Packet
PEG 3350	4 Liters
Senna / Docusate	1 Tablet

EVACUATION PROTOCOL

- Magnesium Citrate 300mL PO x1
- Fleets Enema twice daily for 3 days.
- Polyethylene glycol 4-8 Liters per day until clean

DO NOT USE:

- Milk of Magnesia if GFR < 30

48 – 72 hours of no BM on a stage indicates need for the use of a rescue laxative, and possible increase in stage.

Constipation

Constipation is an often misunderstood, poorly defined side effect of many medications. Due to the prevalence of occurrence with opiates, the link between, and treatment of constipation induced by opiates is relatively well understood. The constipation induced by psychotropic medications is however, far less understood.

Constipation is many different things to many different people. However, Rome-III criteria gives the following definition:

“To have the diagnosis of functional constipation, the patient must satisfy two or more of the following diagnostic criteria:

- a) Straining during at least 25% of defecations
- b) Lumpy or hard stools in at least 25% of defecations
- c) Sensation of incomplete evacuation in at least 25% of defecations
- d) Sensation of anorectal obstruction / blockage for at least 25% of defecations
- e) Manual maneuvers to facilitate at least 25% of defecations
- f) Fewer than three defecations per week”

In a population of known poor informants, it is often difficult to determine the symptoms and complaints regarding constipation. However, it is important to be vigilant in looking for them, as many of the medications used to treat psychosis and their side effects are known to induce constipation. A list of prominent constipating medications is listed later.

Constipation is commonly associated with impaired quality of life, but can have potentially fatal consequences. In a literature review of second generation antipsychotics and constipation, there was a significant amount of data to indicate potentially toxic complications of these medications. These ranged from high rates of untreated constipation to paralytic ileus. Some also reported bowel perforation due to clozapine, gangrenous bowel, fecal impaction, megacolon, and aspiration of feculent vomitus.

Lifestyle Modifications

No matter what the cause of constipation, various measures have been shown to reduce, and possibly even eliminate this problem. First and foremost, increase the hydration status of the individual. While typically unnecessary, individuals who are dehydrated suffer from constipation as a result of their body trying to retain as much water as it can. Restoration of hydration typically cures the incident of constipation, and ensuring they maintain hydration prevents any further bouts. Secondly, most professionals recommend an increase in dietary fiber. Due to the processed nature of most of our foods, our typical fiber intake is far less than the recommended 25g daily intake. Most fiber should come in the form of food; however fiber supplementation can provide benefit to those who cannot achieve this. Lastly, and most importantly, increased exercise has been shown to support many aspects of health. Exercise promotes well-being, decreases stress, and promotes colonic movement. By increasing exercise, you promote overall health, as well as symptom relief and prevention of constipation. These three aspects, and in particular exercise, should form the backbone of any treatment of constipation – be it acute, occasional, or chronic.

Description of All Available Agents:

- **Benefiber**
 - Also known as Partially Hydrolyzed Guar Gum (PHGG), Resource Benefiber is a soluble, non-viscous fiber supplement that has been proven effective in the treatment of acute and chronic constipation. It is inexpensive, effective, and our fiber of choice.
- **Bisacodyl (Dulcolax)**
 - Described as a stimulant laxative, it functions by directly inducing colonic peristalsis. It is metabolized by brush border enzymes, with the active metabolite acting on the mucosa of the intestine. Highly effective at inducing bowel movements, it also slightly softens them by peristalsis. However, it is commonly given in conjunction with a stool softener.
- **Docusate (Colace)**
 - A common stool softener, it functions as a surfactant, facilitating the mixture of fat and water. By assisting in combining water and stool fat, it 'softens' the stool. This provides a literally 'softer' stool, decreasing straining and discomfort associated with hard stool.
- **Lactulose**
 - A sugar that is poorly absorbed by the intestine, and has no enzyme capable of breaking it down in the intestine. It thus reaches the colon relatively unchanged, where flora then break it down into lactic acid. This causes an increase in osmotic pressure, increasing stool water content, softening it. It also increases the frequency of bowel movements.
- **Metamucil**
 - A brand name form of psyllium, a husk of the seed plantago ovata. Functioning as a bulk laxative, studies have indicated that it increases stool frequency, consistency, and ease of evacuation.
- **Mineral Oil**
 - A heavy oil. When drank in sufficient quantities, it coats the bowel (and stool) with a hydrophobic film. This helps retain moisture in the lumen as well as the stool. This stimulates a bowel movement as well as easing evacuation. Contraindicated for long-term use due to toxic build up, and inhibition of absorption of several nutrients.
- **Magnesium Citrate**
 - An osmotic laxative, it works by generating an osmotic gradient to pull water from surrounding tissues. The increased retention distends the colon, causing increased peristaltic activity. It should not be given to individuals with renal impairment due to potentially toxic magnesium accumulation.
- **Magnesium Hydroxide (Milk of Mag)**
 - A hyperosmotic laxative, it works by generating an osmotic gradient to pull water from surrounding tissues. By indiscriminately pulling water from surrounding tissues, it is effective in rapidly emptying the lower intestine and bowel. It however also increases the risk of dehydration and electrolyte abnormalities. It should not be given to individuals with renal impairment due to potentially toxic magnesium accumulation.

- **Polyethylene Glycol 3350 (Miralax)**
 - A widely studied polyether compound, it functions as an osmotic laxative. By increasing the osmotic gradient, it stimulates the movement of water into the lumen of the intestine. Doing such encourages more water to remain in the intestine, forming a softer, easier to pass stool, while prompting a bowel movement.
- **Sennosides (Senokot)**
 - Plant compounds found in the Senna family. They are anthraquinone derivatives, and work by stimulating the nerve endings in the colon. In doing such, they force the muscles to contract more often and with more force (increase peristalsis), prompting a bowel movement. Found to be particularly effective in the treatment of opiate-induced constipation.

PROMINENT CONSTIPATING MEDICATIONS

Aripiprazole (13%)	Fluvoxamine	Perphenazine
Baclofen	Gabapentin	Phenytoin
Benzotropine	Haloperidol	Piroxicam
Bromocriptine	Hydrocodone	Pregablin
Celecoxib	Lamotrigine	Prochlorperazine
Chlorpromazine	Levetiracetam	Quetiapine (9%)
Clozapine (14%)	Loxapine	Risperidone (7-13%)
Codeine	Memantine (5%)	Sertraline
Diphenhydramine	Meperidine	Thioridazine
Divalproex (4%)	Morphine Sulfate	Tizanidine
Escitalopram	Naproxen	Topiramate
Ferrous Sulfate	Olanzapine (9-11%)	Trifluoperazine
Fluoxetine	Oxycodone	
Fluphenazine	Paroxetine	

Constipation Protocol: Works Cited

1. Chatoor, D., Emmanuel, A. Constipation and Evacuation Disorders. *Best Practice & Research Clinical Gastroenterology*. 23 (2009) 517-30
2. Emmanuel, A., Tack, J., Quigley, E., Talley, N. Pharmacological Management of Constipation. *Neurogastroenterol Motil* (2009) 21 (suppl. 2), 41-54
3. De Hert, M., et al. Second-Generation Antipsychotics and Constipation: A Review of the Literature. *European Psychiatry* (2010).
4. Giannini, E., Mansi, C., Dulbecco, P., Savarino, V. Role of Partially Hydrolyzed Guar Gum in the Treatment of irritable Bowel Syndrome. *Nutrition* 22 (2006) 334-342.
5. Longstreth, G., et. al. Rome 3: Functional Bowel Disorders. *Gastroenterology* 2006; 130:1480-1491.
6. McCallum, I., Ong, S., Mercer-Jones, M. Chronic Constipation in Adults. *BMJ*, 28 Mar 2009. 338 (763-6).
7. Mihaylov, S., et. al. Stepped Treatment of Older Adults on Laxatives. The STOOL Trial. *Health Technology Assessment* 2008; 12(13).
8. Mueller-Lissner, S. The Pathophysiology, Diagnosis, and Treatment of Constipation. *Dtsch Arztebl Int* 2009; 106(25): 424-32
9. National Institute of Diabetes and Digestive and Kidney Diseases. (2007). Constipation. (NIH Publication No. 07-2754).
10. Ternent, C., et. al. Practice Parameters for the Evaluation and Management of Constipation. *Dis Colon Rectum* 2007; 50: 2013-2022.

Table 2. MHC's Strategies to Treat Clozapine Hypersalivation

Treatment Option	Mechanism for Reduction of Saliva	Dosage Range	Notes
Anticholinergic Medications			
Benztropine Tablet	Muscarinic receptor antagonist	0.5-6mg daily	Increased risk of constipation
Atropine eye drops		1% place 1-6 drops sublingually daily	Needs multiple daily dosing Minimal systemic absorption Tell patient to swish drops around mouth if possible
Ipratropium Bromide Nasal Spray		0.03-0.06%, 2-6 sprays daily sublingually	Minimal systemic absorption Well tolerated Effect may not be long lasting, requiring multiple daily doses
Pirenzepine Tablet		25-100mg daily	Not available in the United States Side effects: Mild diarrhea may be common Does not cross blood-brain barrier
Trihexyphenidyl Tablet		2-15mg daily	Increased risk of constipation
Hyoscine (scopolamine)		0.4-0.8mg tablet daily 1.5mg patch every 72 hours	Patch was studied with greater improvement than that reported with oral treatment
Amitriptyline Tablet		25-100mg daily	Increased risk of constipation
Biperiden Tablet		6mg daily	Not available in the United States
Glycopyrrolate Tablet or Solution		1-8mg daily	Does not cross blood-brain barrier and may have less impact on cognitive functioning
Alpha₂-Adrenergic Antagonists			
Clonidine	Alpha ₂ -adrenergic receptor antagonist	0.05-0.1mg daily 0.1-0.2mg patch weekly	Postural hypotension may worsen in combination with clozapine
Terazosin Capsule		2mg at bedtime	Other side effects: Hypotension, sedation, dizziness, urinary retention, bradycardia, constipation
Guanfacine Tablet		1mg daily	
Other Treatments			
Sulpiride Tablet	Unknown, selectively binds D ₂ and D ₃ receptors	150-300mg daily	Not available in the United States May allow for decrease in clozapine dosage which can reduce hypersalivation
Amisulpride Tablet		400mg daily	
Botulinum Toxin	Inhibits acetylcholine release in salivary glands	150 international units injected into parotid glands	Side effects: pain, tenderness, bleeding RARE: jaw dislocation

NOTE: none of these treatment options are FDA approved for this indication and there are not established doses for this purpose.

Anticholinergic Medications

Contraindications: narrow-angle glaucoma, bladder obstruction, prostatic hypertrophy, and gastrointestinal motility disorders

Adverse effects: dry mouth, urinary retention, blurred vision, impairment in cognitive functioning