VA | U.S. Department of Veterans Affairs

Clinical Pearls to Manage Clozapine

A Quick Reference Guide

[Provider]

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

VA PBM Academic Detailing Service

Real Provider Resources

Real Patient Results

Your Partner in Enhancing Veteran Health Outcomes

VA PBM Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

VA PBM Academic Detailing Service SharePoint Site:
https://vaww.portal2.va.gov/sites/ad

Table of Contents

Clozapine Initiation and Titration[1,2]*							
Week 1	AM (mg)	PM (mg)	TOTAL (mg)	Week 2	AM (mg)	PM (mg)	TOTAL (mg)
Day 1	0–12.5	12.5	12.5–25	Day 8	50	100	150
Day 2	0–12.5	12.5–25	25	Day 9	100	100	200
Day 3	25	25	50	Day 10	100	100	200
Day 4	25	50	75	Day 11	50	200	250
Day 5	50	50	100	Day 12	50	200	250
Day 6	50	75	125	Day 13	100	200	300
Day 7	50	100	150	Day 14	100	200	300

*Titration recommendations above are guidelines only. Individual patient characteristics should be considered and dosing should be adjusted accordingly. Patients experiencing dose related side effects such as over sedation or orthostasis may require longer intervals between dose increases.

- Dose may be consolidated into once daily dosing; after day 14 subsequent dose increase should not be made more than once or twice a week in increments not to exceed 100 mg (target dose 300–450 mg/day in divided doses by the end of 2 weeks);
- Must be re-titrated if not taken for >48 hours (see Clozapine Plasma Levels on page 2 for additional information)

Clozapine Plasma Levels[3,4]	
Suggested level:	350–550 ng/mL
Relapse more likely if level:	<200 ng/mL or reduced 40–60%
Levels affected by:	Concomitant medications: can increase or decrease levels; see drug interactions table (on pages 4 through 7)
	Smoking: decreases clozapine level; clozapine dose reduction should be considered if patient quits smoking
	Gender: higher levels seen in females vs males
	Age: increase age = increase clozapine level
	Caffeine: increases clozapine levels; heavy caffeine drinkers may need lower clozapine doses

Restarting Clozapine[2]*	
Time Since Last Dose	**Recommendation for Restarting**
<48 hours since last dose	Restart at previous dose, no titration needed
48–72 hours since last dose	Rapid Re-titration • **Day 1**: Begin with half the previously prescribed total daily dose (given in divided doses 12 hours apart) • **Day 2**: Increase to 75% of previous total daily dose (in divided doses 12 hours apart) • **Day 3**: If tolerated, resume previous dose
72 hours – 7 days	Re-titration with 12.5 mg or 25 mg – increase dose over ≥3 days as tolerated to previous dose
>7 days	Consider patient a new patient and titrate dose accordingly – previous dose should be reached within 3–4 weeks

*If treatment is interrupted for <30 days, continue ANC monitoring as before; if treatment is interrupted for ≥30 days, monitor ANC as if new patient

Clozapine and Pharmacokinetic Interactions[5–11,4]*			
	CYP 450	Interaction	Notes
Increases Clozapine Levels (Inhibitors)	**CYP 1A2****	• Caffeine (increases 15–20%) • Ciprofloxacin (increases 30%) • Erythromycin • Fluvoxamine (increases 500–1000%) • Oral contraceptives	• Decrease clozapine dose to 1/3 of the original dose when given with strong CYP1A2 inhibitors (e.g., fluvoxamine or ciprofloxacin). - Please note: for episodic use of strong inhibitors (e.g. ciprofloxacin) clozapine dose should be increased back to original dose after inhibitor is discontinued. • Weak-moderate inhibitors (e.g. oral contraceptives, caffeine) may require increased monitoring to determine if dose adjustment is needed.

*For complete information on interactions (list of drugs, timing of interaction, monitoring/management recommendations, please see clozapine package insert; **Primary route of metabolism

continued

Clozapine and Pharmacokinetic Interactions[5–11,4]*			
	CYP 450	Interaction	Notes
Increases Clozapine Levels (Inhibitors)	**CYP 2D6**	• Amiodarone • Bupropion • Duloxetine • Escitalopram • Fluoxetine (increases 40–70%) • Paroxetine (increases 20–40%) • Sertraline (no effect <100 mg)	Concomitant treatment with CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, paroxetine, fluoxetine, or sertraline) can increase clozapine levels. Use caution and monitor patients closely to determine if dose reduction is needed.

*For complete information on interactions (list of drugs, timing of interaction, monitoring/management recommendations, please see clozapine package insert

continued

Clozapine and Pharmacokinetic Interactions[5–11,4]*			
	CYP 450	**Interaction**	**Notes**
Increases Clozapine Levels (Inhibitors)	**CYP 3A4**	• Amiodarone • Cimetidine (increases 50–100%) • Ciprofloxacin (increases 30%) • Erythromycin • Ketoconazole	—
Decreases Clozapine Levels (Inducers)	**CYP 1A2****	• Carbamazepine (decreases 50%) • Omeprazole • Phenobarbital (decreases 35%) • Smoking (decreases 50%) • Rifampin	• Caution: Smoking cessation in a patient on clozapine may cause the patient's plasma clozapine level to increase 1.5x 2–4 weeks later. - Dose related adverse events possible (e.g. seizures) if dose not reduced

*For complete information on interactions (list of drugs, timing of interaction, monitoring/management recommendations, please see clozapine package insert; **Primary route of metabolism

continued

Clozapine and Pharmacokinetic Interactions[5–11,4*]			
	CYP 450	**Interaction**	**Notes**
Decreases Clozapine Levels (Inducers)	**CYP 2D6**	Rifampin	—
	CYP 3A4	• Carbamazepine (decreases 50%) • Phenobarbital (decreases 35%) • Phenytoin • Rifampin	Concomitant use with strong CYP3A4 inducers (carbamazepine, phenytoin, or rifampin) is not recommended.

Valproic acid has been reported to both increase and decrease clozapine levels by an unknown mechanism. One study suggested that smokers who take valproic acid experience a decrease in clozapine levels and non-smokers who take valproic acid experience increased levels[10,11]; *For complete information on interactions (list of drugs, timing of interaction, monitoring/management recommendations, please see clozapine package insert

Pharmacodynamic Interactions[1,12]	
Anticholinergic Effects	Clozapine has a high rate of anticholinergic side effects such as constipation, fecal impaction, urinary retention, sedation, and tachycardia. Caution is advised before adding additional medications with moderate to strong anticholinergic effects. Patients should be monitored for increased anticholinergic side effects.
Severe Neutropenia	Clozapine has a Black Box Warning and required blood monitoring due to its risk for severe neutropenia. Caution is advised before adding medications known to cause neutropenia (e.g. carbamazepine) as they may increase risk of this adverse event.
Hypotension, Bradycardia, and Syncope	Clozapine has a Black Box Warning due to risk of orthostatic hypotension, bradycardia, and syncope. This risk is highest during the initial titration phase of treatment. Caution is advised before adding or adjusting medications that may affect blood pressure especially during the initial titration of clozapine.
QTc Prolongation	QT prolongation, Torsade de Pointes, cardiac arrest, and sudden death have occurred with clozapine treatment. Caution is advised before adding medications that prolong QTc interval (ziprasidone, erythromycin, moxifloxacin) or that inhibit clozapine metabolism (e.g., fluoxetine, fluvoxamine, or amiodarone). See clozapine package insert for more information.

continued

Pharmacodynamic Interactions[1,12]	
Respiratory Depression	Clozapine used in combination with benzodiazepines has rarely resulted in adverse reactions such as confusion, ataxia, delirium, cardiac/respiratory arrest, and death. If a benzodiazepine is necessary, it is recommended to begin with the lowest possible dose and to closely monitor the patient, particularly at initiation of treatment and following dose increases.
Seizures	Clozapine has a cumulative seizure incidence of 5% at 1 year of treatment. Seizures appear to be dose related and occur more frequently during titration and with high daily doses. Caution is advised before adding medications known to lower the seizure threshold as this may further increase risk of seizures.
Metabolic Syndrome	Clozapine has a high incidence of metabolic side effects. Adding medications known to increase weight, blood glucose, or cholesterol levels should be avoided if possible.

Clozapine and Monitoring Recommendations/Requirements[1,2,13–16]			
	Baseline+	Ongoing Monitoring	
	Parameters to Monitor	Frequency	Parameters to Monitor
Agranulocytosis (Required)	ANC	First 6 months: weekly	ANC
		6–12 months**: every 2 weeks	ANC
		12 months+: every 4 weeks	ANC
Myocarditis	Pulse CRP BP Troponin I/T Temp RR Echo (or ECG) CBC with diff	Daily if possible, at least every 2nd day recommended	Pulse BP Temp RR

+≤30 days prior to clozapine initiation; *Weight should be monitored more frequently; **If ANC remains in normal range (see page on hematologic monitoring for more details); CRP = C-reactive protein; Temp = temperature; BP = blood pressure; CBC = complete blood count; ANC = absolute neutrophil count; ECG = electrocardiogram; AST/ALT = aspartate/alanine aminotransferase; BUN = blood urea nitrogen; SCr = serum creatinine

continued

Clozapine and Monitoring Recommendations/Requirements[1,2,13–16]			
	Baseline+	Ongoing Monitoring	
	Parameters to Monitor	Frequency	Parameters to Monitor
Myocarditis (continued)	Pulse CRP BP Troponin I/T Temp RR Echo (or ECG) CBC with diff	Weekly for first month	CRP CBC with diff Troponin I/T
		At each visit	Chest pain Fever or flu-like symptoms Cough Shortness of breath Exercise capacity/fatigue
Metabolic Syndrome	Weight and height Waist circumference Blood pressure Fasting lipids Fasting blood glucose	Quarterly for 1st year then annually	Weight* Waist circumference Blood pressure Fasting lipids Fasting blood glucose

+≤30 days prior to clozapine initiation; *Weight should be monitored more frequently; **If ANC remains in normal range (see page on hematologic monitoring for more details); CRP = C-reactive protein; Temp = temperature; BP = blood pressure; CBC = complete blood count; ANC = absolute neutrophil count; ECG = electrocardiogram; AST/ALT = aspartate/alanine aminotransferase; BUN = blood urea nitrogen; SCr = serum creatinine

continued

Clozapine and Monitoring Recommendations/Requirements[1,2,13–16]			
	Baseline+	Ongoing Monitoring	
	Parameters to Monitor	Frequency	Parameters to Monitor
Constipation	Check for baseline constipation	• Weekly for first 4 months • At each visit	Ask about bowel habits
Other	AST/ALT	Clinical judgment based on individual patient characteristics	AST/ALT
	BUN/SCr		BUN/SCr
	Pregnancy test		Pregnancy test

+≤30 days prior to clozapine initiation; *Weight should be monitored more frequently; **If ANC remains in normal range (see page on hematologic monitoring for more details); CRP = C-reactive protein; Temp = temperature; BP = blood pressure; CBC = complete blood count; ANC = absolute neutrophil count; ECG = electrocardiogram; AST/ALT = aspartate/alanine aminotransferase; BUN = blood urea nitrogen; SCr = serum creatinine

Clozapine and Select Side Effects[2,17–22]			
Side Effect	**Incidence**	**Additional Info**	**Management Options**
Sedation	Up to 46%	• Most common in the first few months • Usually lessens over time but may persist	• Give smaller clozapine dose in the morning • Give total daily dose at bedtime • Reduce dose if appropriate • Avoid other CNS depressants • Check plasma level

continued

Clozapine and Select Side Effects[2,17–22]			
Side Effect	**Incidence**	**Additional Info**	**Management Options**
Sialorrhea	Varies from 30–50% on average	• Most common in the first few months • May wear off over time • Greatest at night	Nonpharmacologic • Chew sugar-free gum • Sleep with head propped to avoid choking • Place towel on pillow Pharmacologic • Reduce clozapine dose if possible/appropriate • Medications used to manage sialorrhea include*: - Atropine* 1% eye drops 3-4 drops placed under the tongue HS and up to 3 times per day PRN - Benztropine* 1 mg BID - Clonidine patch** (0.1–0.2 mg/day)/ Clonidine oral 0.05–1 mg/day - Glycopyrrolate* **(NF)** 1 mg BID or 2–4 mg HS - Scopolamine* **(NF)** 1.5 mg patch Q 72hrs or 0.3 mg PO HS - Trihexyphenidyl* 5–15 mg HS

*Pharmacotherapy options have limited evidence to support their use can cause additional side effects including anticholinergic side effects;

Monitor blood pressure and for worsening mood and psychosis; **NF = Not currently on VA National Formulary

Clozapine and Select Side Effects[2,17–22]			
Side Effect	**Incidence**	**Additional Info**	**Management Options**
Tachycardia	~25%	Most common in first 4 weeks but may persist; usually benign unless present at rest with fever*, hypotension, or chest pain (may indicate myocarditis)	Pharmacologic • Beta blocker (e.g. atenolol 25–100 mg/day or metoprolol 25–200 mg BID); Hold if blood pressure <100/60 or pulse <60 bpm • Consider referral to cardiologist for work-up • Stop clozapine if tachycardia occurs with chest pain or heart failure
Orthostatic Hypotension	~9%	Most common in first 4 weeks	Nonpharmacologic • Sit and stand up slowly • Avoid dehydration Pharmacologic • Slow titration of clozapine • Reduce clozapine dose if possible/appropriate • Consider other meds that may be contributing to dehydration or orthostasis • Divide doses or give at alternate times from other medications • May consider fludrocortisone in severe cases

*Note, up to 20% of patients may develop a benign and transient fever when starting clozapine; pay close attention to other signs/symptoms that could signal myocarditis

continued

Clozapine and Select Side Effects[2,17–22]			
Side Effect	**Incidence**	**Additional Info**	**Management Options**
Seizures	1–5% (dose dependent)	• Related to plasma level and rapid dose escalation • Tonic clonic, myoclonic seizures most common • Caution with existing seizure disorder, history of head trauma or with other drugs that lower seizure threshold	• Avoid other drugs known to reduce seizure threshold • Discontinue clozapine for 24 hours • EEG and neurology consult advised • Rechallenge once seizures under control – restart a dose of 50% of the seizure-initiating dose - Titrate dose slowly • Consider adding valproate 500 mg or other anticonvulsant (e.g. lamotrigine, topiramate) and titrate to effectiveness**

**Caution: valproic acid may alter clozapine levels

Clozapine and Select Side Effects[2,17–22]			
Side Effect	**Incidence**	**Additional Info**	**Management Options**
Urinary Incontinence	Up to 20%	• May occur at any time during treatment; may resolve spontaneously but may persist for months or years • Nocturnal is most common	Nonpharmacologic • Avoid fluids before bed Pharmacologic • Consider clozapine dose reduction or changing schedule to avoid periods of deep sedation • Medication management options are not strongly supported by literature (e.g. desmopressin)
Thromboembolism	Rare, but has resulted in fatalities	PE and DVT have occurred in patients treated with clozapine.	Consider the possibility of pulmonary embolism in patients who present with DVT, acute dyspnea, chest pain, or with other respiratory signs and symptoms.

PE = pulmonary embolism; DVT = deep-vein thrombosis

Clozapine-induced Myocarditis[2,13,23,24]			
Incidence	**Factors that increase risk**	**When to stop clozapine**	**What to do if you suspect myocarditis**
• 0.7–3% • Risk greatest within 1st month but can occur anytime during treatment	• Rapid dose increases • Valproate • Other medications associated with myocarditis (e.g. lithium, risperidone, haloperidol) • Older age	• Signs of heart failure or illness • Troponin >2x upper limit of normal • CRP >100 mg/L	• Discontinue clozapine • Consult cardiology (repeat ECG) • Provide supportive care • Rechallenge is not recommended if myocarditis is confirmed

Signs and Symptoms of Myocarditis[2]*	
Signs	ECG changes, enlarged heart on radiography/echo, eosinophilia
Symptoms	Hypotension, tachycardia, fever, flu-like symptoms, fatigue, dyspnea (with increased respiratory rate), chest pain

*Symptoms of myocarditis can occur in patients on clozapine but do not have myocarditis, while the absence of symptoms does NOT rule out myocarditis

continued

Monitoring Recommendations[2,14]*		
Baseline	**Weekly (Days 7, 14, 21, 28)**	**At each visit, ask about:**
Pulse**	CBC with diff	Chest pain
BP**	CRP	Fever or flu-like symptoms
Temp**	Troponin I/T	Cough
RR**		Shortness of breath
CRP		Exercise capacity/fatigue
Troponin I/T		
Echo or ECG		
CBC with diff		

*Monitoring should be done more closely in the first few months of treatment; consider baseline ECG and if symptomatic;
**Monitor daily if possible, at least every second day recommended;
CRP = C-reactive protein; Temp = temperature; BP = blood pressure; CBC = complete blood count; ECG = echocardiogram

Clozapine-induced Gastrointestinal Hypomotility (CIGH)[2,13,15]

- Constipation: common in patients on clozapine (up to 60% of patients)
- CIGH = impaired motility throughout the gastrointestinal system; can cause dysphagia, ileus, intestinal obstruction, bowel ischemia and megacolon
  - ~36% of cases occur during the first 4 months of clozapine use
  - Fatality rate for patients with CIGH ~20–30%
  - Clozapine doses were higher among those who died (mean dose = 535 mg/day)

Monitoring	Check for pre-existing constipation; adequately treat before starting clozapine
	Ask about bowel habits weekly for the first 4 months and routinely thereafter (note: normal bowel habits may vary) • Abdominal exam indicated if baseline bowel habits change or <3 bowel movements per week
	Signs and symptoms of CIGH: moderate to severe abdominal pain, abdominal distension, vomiting, absent bowel sounds
Prevention/ Management	Educate patients about: • Risks of constipation • Proper diet (increase fiber intake) and adequate fluid intake (fluid intake should be increased if fiber intake is increased: 1.5–2 L/day); consider referral to dietician for assistance • Regular exercise (~150 mins/week if able)

continued

Clozapine-induced Gastrointestinal Hypomotility (CIGH)[2,13,15]	
Prevention/ Management (continued)	Avoid prescribing concomitant medications also known to cause or worsen constipation (e.g. opioids, anticholinergics)
	Slow clozapine titrations (not exceeding 25 mg/day or 100 mg/week) may reduce risk
	Stimulant laxatives and stool softeners (e.g. senna + docusate titrated as needed) to manage constipation; 2nd line treatment: lactulose, polyethylene glycol
Treatment of Acute CIGH	Stop clozapine
	Assess for bowel obstruction (consider gastroenterology consult) • If no obstruction: consider enema or digital disimpaction • If obstruction present: urgent surgical referral needed (or refer to emergency room)
Pearls of Treatment	Bulk laxatives and high fiber diets are contraindicated in patients with obstructive symptoms, megacolon, or megarectum
	Long-term stimulant laxative use not recommended
	If intestinal obstruction is suspected or present, avoid stimulant laxatives and refer patient to medicine
	Lactulose can take up to 72 hours to work; not appropriate if need for treatment is urgent

Calculating Absolute Neutrophil Count (ANC)[1]

ANC equals the total WBC count multiplied by the total percentage of neutrophils (segs plus bands):

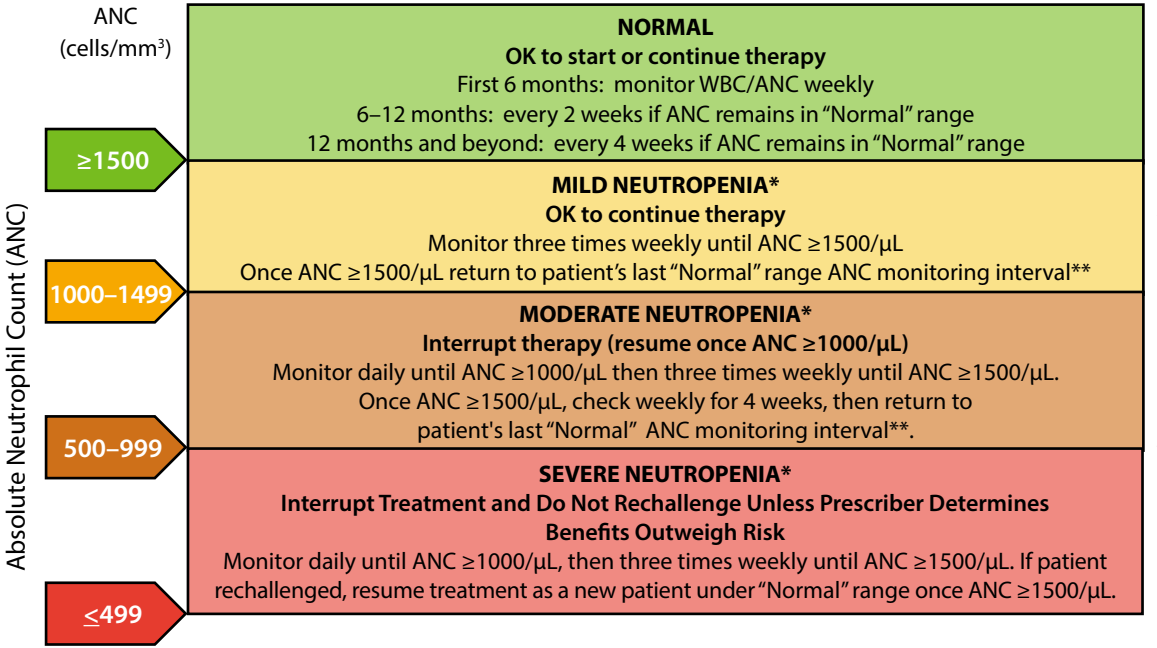
$$\textbf{ANC} = \textbf{WBC (mm}^3\textbf{)} \times \frac{\textbf{(\% Neutrophils)}}{\textbf{100}}$$

Example:
WBC = 4.3; Segs = 48%; Bands = 2%
ANC = 4300 x (0.48 + 0.02) = 4300 x 0.5
ANC = 2150

An online ANC calculator can be found at
http://www.globalrph.com/anc.htm

General Guidelines for Management of All Patients with Fever or with Neutropenia[1]
• Fever is often the first sign of neutropenic infection
• Interrupt clozapine as a precautionary measure in patients who develop fever (38.5°C [101.3°F] or greater), and obtain an ANC
• If fever occurs in any patient with an ANC less than 1000/µL, initiate appropriate workup and treatment for infection and follow treatment recommendations and monitoring protocols

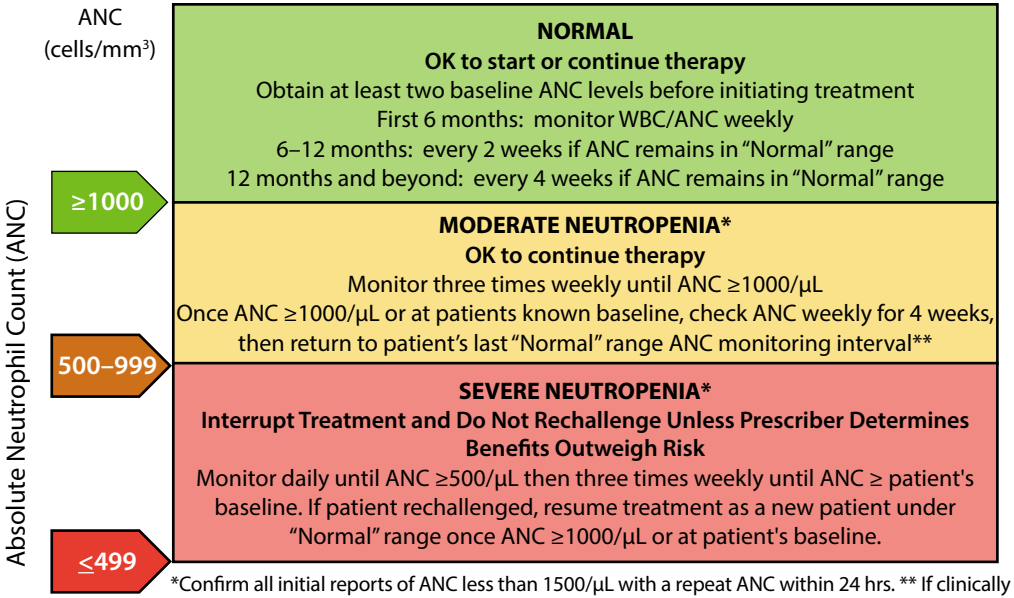
Clozapine and Frequency of Hematologic Monitoring: General Population[1]



* Confirm all initial reports of ANC less than 1500/µL with a repeat ANC within 24 hrs.

** If clinically appropriate; Hematology consultation recommended for moderate and severe neutropenia.

Clozapine and Frequency of Hematologic Monitoring: Benign Ethnic Neutropenia (BEN)[1]



*Confirm all initial reports of ANC less than 1500/µL with a repeat ANC within 24 hrs. ** If clinically appropriate; Hematology consultation recommended for moderate and severe neutropenia.

- Benign ethnic neutropenia (BEN) is a condition where ANC values are lower than "standard" laboratory ranges for neutrophils.
- BEN is commonly observed in individuals of African descent (25–50%) and some Middle Eastern ethnic groups
- BEN is more common in men
- Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation
- BEN patients are healthy and do not suffer from repeated or severe infections
- **They are not at increased risk for developing clozapine-induced neutropenia**
- Additional evaluation may be needed to determine if baseline neutropenia is due to BEN thus hematology consultation is recommended

Clozapine Medication Augmentation Strategies[25–34]		
Medication	**Studied Augmentation Dose**	**Comments**
Antipsychotics		
Risperidone	6mg/day	• Literature does not support one antipsychotic over another • Efforts typically combine different mechanisms of action and/or receptor affinities • Benefits of augmentation in meta-analyses have been found to be minimal at most
Ziprasidone	80 mg/day = most studied; may dose up to ~ 130 mg/day	
Aripiprazole	7.5 mg – 15 mg/day	
Antidepressants		
Citalopram	20 mg/day	• SSRIs can increase clozapine levels • Mirtazapine and citalopram may be the best antidepressants to improve negative symptoms when combined with clozapine • Major interaction for fluvoxamine + clozapine due to CYP 1A2 inhibition leading to increased clozapine exposure; reduce clozapine dose by 1/3[8]
Fluvoxamine	25–50 mg/day (measure clozapine levels)	
Mirtazapine	30 mg/day	

continued

Clozapine Medication Augmentation Strategies[25–34]		
Medication	**Studied Augmentation Dose**	**Comments**
Mood Stabilizers/Anticonvulsants		
Lamotrigine	200 mg/day	• Meta-analysis found improvements noted with lamotrigine and topiramate diminish when outlier studies were removed
Topiramate	200 mg/day	
Lithium	800 mg/day	• Limited evidence suggests that lithium improves symptoms only for schizoaffective patients
Divalproex	1000 mg – 2000 mg/day	• Valproate showed general improvement in a retrospective analysis*

*Caution: valproic acid may alter clozapine levels

References

1. Novartis Pharmaceuticals Corp., *Clozaril (clozapine) [package insert]*. 2015: Rosemont, PA, USA.
2. Taylor, D., C. Paton, and S. Kapur, *Prescribing guidelines in psychiatry*. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust, 2012.
3. Rostami-Hodjegan, A., et al., *Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients*. J Clin Psychopharmacol, 2004. 24(1): p. 70–8.
4. de Leon, J., *Atypical antipsychotic dosing: the effect of smoking and caffeine*. Psychiatr Serv, 2004. 55(5): p. 491–3.
5. Haslemo, T., et al., *The effect of variable cigarette consumption on the interaction with clozapine and olanzapine*. Eur J Clin Pharmacol, 2006. 62(12): p. 1049–53.
6. Hagg, S., et al., *Effect of caffeine on clozapine pharmacokinetics in healthy volunteers*. Br J Clin Pharmacol, 2000. 49(1): p. 59–63.
7. Raaska, K. and P.J. Neuvonen, *Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia*. Eur J Clin Pharmacol, 2000. 56(8): p. 585–9.
8. Raaska, K., et al., *Effect of caffeine-containing versus decaffeinated coffee on serum clozapine concentrations in hospitalised patients*. Basic Clin Pharmacol Toxicol, 2004. 94(1): p. 13–8.
9. Spina, E., et al., *Plasma concentrations of clozapine and its major metabolites during combined treatment with paroxetine or sertraline*. Pharmacopsychiatry, 2000. 33(6): p. 213–7.

continued

10. Spina, E. and J. de Leon, *Clinically relevant interactions between newer antidepressants and second-generation antipsychotics*. Expert Opin Drug Metab Toxicol, 2014. 10(5): p. 721–46.
11. Yoshinari, K., et al., *Omeprazole transactivates human CYP1A1 and CYP1A2 expression through the common regulatory region containing multiple xenobiotic-responsive elements*. Biochem Pharmacol, 2008. 76(1): p. 139–45.
12. Bitter, R., T.L. Demler, and L. Opler, *Safety evaluation of the concomitant use of clozapine and benzodiazepines: a retrospective, cross-sectional chart review*. J Psychiatr Pract, 2008. 14(5): p. 265–70.
13. Nielsen, J., et al., *Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided?* J Clin Psychiatry, 2013. 74(6): p. 603–13; quiz 613.
14. De Berardis, D., et al., *Update on the adverse effects of clozapine: focus on myocarditis*. Curr Drug Saf, 2012. 7(1): p. 55–62.
15. Palmer, S.E., et al., *Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases*. J Clin Psychiatry, 2008. 69(5): p. 759–68.
16. MIRECC, M.I.R.E.C.C., *MIAMI: MIRECC Initiative on Antipsychotic Management Improvement*. **http://www.mirecc.va.gov/miamiproject**.
17. Goldberg, J. and C. Ernst, *Managing the Side Effects of Psychotropic Medications*. 2012, Arlington, VA: American Psychiatric Publishing.
18. Perry, P.J., *Psychotropic drug handbook*. eighth ed. 2007, Philadephia, PA: Lippincott Williams & Wilkins.
19. Williams, A.M. and S.H. Park, *Seizure associated with clozapine: incidence, etiology, and management*. CNS Drugs, 2015. 29(2): p. 101–11.

continued

20. Praharaj, S.K., M. Arora, and S. Gandotra, *Clozapine-induced sialorrhea: pathophysiology and management strategies*. Psychopharmacology, 2006. 185(3): p. 265–273.
21. Lieberman, J.A., *Maximizing clozapine therapy: managing side effects*. J Clin Psychiatry, 1998. 59 Suppl 3: p. 38-43.
22. Annamraju, S., et al., *Early recognition of clozapine-induced myocarditis*. Journal of clinical psychopharmacology, 2007. 27(5): p. 479–483.
23. Ronaldson, K.J., P.B. Fitzgerald, and J.J. McNeil, *Clozapine-induced myocarditis, a widely overlooked adverse reaction*. Acta Psychiatr Scand, 2015. 132(4): p. 231–40.
24. De Fazio, P., et al., *Rare and very rare adverse effects of clozapine*. Neuropsychiatr Dis Treat, 2015. 11: p. 1995–2003.
25. *Aripiprazole. Clinical Pharmacology [database online]*. Gold Standard, Inc.
26. Van Sant, S.P. and P.F. Buckley, *Pharmacotherapy for treatment-refractory schizophrenia*. Expert Opin Pharmacother, 2011. 12(3): p. 411–34.
27. Muscatello, M.R., et al., *Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study*. J Psychopharmacol, 2011. 25(5): p. 667–74.
28. Muscatello, M.R., et al., *Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study*. J Clin Psychopharmacol, 2014. 34(1): p. 129–33.
29. Zoccali, R., et al., *The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study*. Int Clin Psychopharmacol, 2004. 19(2): p. 71–6.

continued

30. **Mossaheb, N., et al., *Favourable results in treatment-resistant schizophrenic patients under combination of aripiprazole with clozapine*. World J Biol Psychiatry, 2010. 11(2 Pt 2): p. 502–5.**
31. **Borba, C.P. and D.C. Henderson, *Citalopram and clozapine: potential drug interaction*. J Clin Psychiatry, 2000. 61(4): p. 301–2.**
32. **Polcwiartek, C. and J. Nielsen, *The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review*. Psychopharmacology (Berl), 2016. 233(5): p. 741–50.**
33. **Tracy, D.K., et al., *Skating on thin ice: pragmatic prescribing for medication refractory schizophrenia*. BMC Psychiatry, 2015. 15: p. 174.**
34. **Dold, M. and S. Leucht, *Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective*. Evid Based Ment Health, 2014. 17(2): p. 33–7.**

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

VA PBM Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

VA PBM Academic Detailing Service SharePoint Site:
https://vaww.portal2.va.gov/sites/ad

Created July 2016

IB 10-758, P96761 **www.va.gov**