Guidelines for Prescribing and Monitoring Clozapine

Purpose: To provide a structured approach for the safe and effective use of clozapine in treating treatment-resistant schizophrenia (TRS) and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Indications:

1. FDA-approved indications:
    - Treatment-resistant schizophrenia
        - For severely ill patients who do not respond adequately to other antipsychotic treatment.
    - Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder
        - Of note: currently the *only* anti-psychotic FDA-approved for suicide prevention.
2. Non-FDA uses (with supporting evidence):
    - Psychosis co-occurrent with and due to Parkinson's disease (per Micromedex)
    - Managing aggressive behavior in schizophrenia (per MD Quanbeck)
    - Consider for patients with symptoms partially or fully resistant to other antipsychotics or accompanied by persistent suicidal or self-injurious behavior. Other indications include sensitivity to extrapyramidal symptoms and tardive dyskinesia. Clozapine does not need to be reserved as a treatment of last resort and can be considered after 2-3 failed antipsychotic trials based on clinical judgment.

Initiating Treatment:

1. Conduct a comprehensive baseline assessment, including:
    - General and cardiovascular health status
    - Pro Tip: Utilize REMS JobAid
        - https://www.newclozapinerems.com/Public/home/Prescriber
        - See: Enrollment & Lab procedures with nursing support
    - CBC with differential, metabolic panel, lipid panel, HbA1c, and vital signs
    - ECG
        - Particularly in elderly population to document existing abnormalities that might incorrectly be identified as “clozapine-induced” & disrupt treatment.
    - Baseline body habitus: weight, height, & waist circumference
    - Standard of Care for anti-psychotics (i.e., AIMS, serum levels, pregnancy test)
    - Baseline troponin & high sensitivity C-reactive protein (CRP) due to significant risk of myocarditis
2. Ensure no contraindications are present and obtain informed consent after discussing benefits & risks.
3. Discontinue contraindicated medications:
    - Benzodiazepines (risk of cardiorespiratory collapse)
    - Carbamazepine (increased risk of neutropenia)
    - Ciprofloxacin (dramatically increases clozapine levels, leading to toxicity)
        - Add “ciprofloxacin allergy while on clozapine due to DDI"

4. Initiate clozapine at 12.5-25 mg/day (12.5 mg test dose for first-time users), titrating slowly based on tolerability and setting (inpatient vs. outpatient)
    - Continue taper of non-clozapine anti-psychotics while titrating up clozapine.
5. Monitor for therapeutic response and adverse effects over a 6-month trial period
6. Check clozapine levels 5 days after completing titration, aiming for 350-600 ng/mL (minimum therapeutic threshold is 100 ng/mL; point of futility > 1000 ng/mL)

Dosage and Titration:

- Initial target dose: 300-450 mg/day (150 mg/day if co-administered with fluvoxamine)
- Maximum dose: 900 mg/day
- Fluvoxamine co-administration with clozapine
    - Clozapine is metabolized into norclozapine by CYP450 1A2 enzymes
    - Norclozapine is thought to be associated with metabolic adverse effects, such as weight gain and dyslipidemia
    - Fluvoxamine is a strong CYP450 1A2 inhibitor
    - To increase the clozapine to norclozapine ratio, initiate fluvoxamine at 25 mg qhs and increase dose by 25 mg as tolerated over 1 – 3 days to 150 mg
    - Effect: therapeutic levels attained at 150 mg clozapine that are on average equal to 350 mg of clozapine treatment without fluvoxamine.
    - May consider fluvoxamine if clinically appropriate (note different titration schedule for coadministration).

    Note: The practice of adding fluvoxamine to clozapine and monitoring the clozapine to norclozapine ratio (CLZ:NDMC) may not be standard across all settings. Potential disruptions can occur if patients are transferred to settings that do not follow this practice.

- **Setting**: Non-urgent, outpatient (slow titration)
    - Start at 12.5 – 25 mg daily QHS for 3 days
    - Continue to titrate up 25 mg daily until target dosage is reached
- **Setting**: Urgent, inpatient, medically-supervised (fast titration)
    - *Without fluvoxamine* - Follow below titration schedule:

Day	Dosage
1	12.5 mg bid
2	25 mg am
3	25 mg bid
4	25 mg am + 50 mg hs
5	50 mg bid
6	50 mg am + 75 mg hs

Day	Dosage
7	50 mg am + 100 mg hs
8	50 mg am + 100 mg hs
9	100 mg bid
10	100 mg bid
11	50 mg am + 200 mg hs
12	50 mg am + 200 mg hs
13	100 mg am + 200 mg hs
14	100 mg am + 200 mg hs

    - *With fluvoxamine* - Start at 25 mg and titrate up by 25 mg daily until 150 mg dosage reached
- Slower titration and lower doses may be necessary for older patients or those with cardiac issues
- Adjust dosage for individuals of Asian descent, who typically require lower doses

- Consider dividing doses if excessive sedation or other side effects (enuresis, AM grogginess) occur

Monitoring:

- Hematological monitoring per Clozapine REMS guidelines
  - Weekly for the first 6 months, biweekly for the second 6 months, then monthly
  - See: Enrollment & Lab procedures with nursing support
  - Manage neutropenia based on absolute neutrophil count (ANC) thresholds
    - Normal: 1.5 – 8 x 10^3/µL
    - Mild: 1 – 1.499 x 10^3/µL
      - Increase monitoring to three times/week until ANC > 1.5 x 10^3/µL)
    - Moderate: 0.5 – 0.999 x 10^3/µL
      - Clozapine interruption and daily monitoring until ANC reaches 1 x 10^3/µL and then clozapine can be resumed
    - Severe: Less than 0.5 x 10^3/µL
      - Discontinue clozapine and increase ANC monitoring
      - Can resume when ANC > 1.5 x 10^3/µL if benefits greatly outweigh risks
  - Confirmatory tests within 24 hours if ANC < 1.5 10^3/µL
  - The formula for the ANC calculation is:
    ANC = WBC count × (percentage of segs + percentage of bands) or
    ANC = WBC count × [(number of segs + number of bands) / 100]
    - WBC count is usually in cells per microliter (cells/µL)
    - The percentage of segs and bands is given in the differential count as a percentage
  - Treating agranulocytosis: filgrastim can expedite ANC recovery; however, its impact on infection rates and mortality is unclear
    Of Note: a significant portion of African-Americans have benign ethnic neutropenia resulting in lower utilization and higher rates of discontinuation despite being less likely to develop severe neutropenia
- Metabolic monitoring:
  - Weight, waist circumference, blood pressure, fasting glucose or HbA1c, and lipid panel at regular intervals
  - Manage abnormalities through lifestyle modifications and pharmacological interventions (metformin and/or topiramate, GLP-1 receptor agonists, or co-administration with fluvoxamine)
    Of Note: lower metabolic risks than olanzapine
- Cardiovascular monitoring:
  - Monitor for myocarditis, particularly during first 4-8 weeks of treatment
  - Each visit, assess for symptoms & check vital signs
  - Weekly troponin I & high sensitivity CRP for the first 8 weeks
    - If Troponin I not available, monitor troponin T (less specific)
    - CRP > 100 mg/L and troponin > twice the normal limit are critical indicators of clozapine-induced myocarditis in symptomatic patients
    - Eosinophil count may rise as well, but less consistent and delayed

- Perform echocardiography if myocarditis or cardiomyopathy is suspected
    - Standard ECG monitoring on clozapine: baseline and annual. Risk for QTc interval prolongation
    - ECG key for assessing ventricular and valve function with suspected myocarditis/cardiomyopathy
- Monitor for orthostatic hypotension, bradycardia, and syncope

- Seizure monitoring:
    - Inquire about seizure history and monitor for myoclonic jerking
    - If a seizure occurs, hold clozapine for 24 hours, reduce the dose by 50%, and consider adding an anticonvulsant
        - Divalproex/Valproic acid (VPA): Load 30 mg/kg over 24 hours. Can exacerbate weight gain and carries an increased risk of developing neutropenia. Effective for both generalized and myoclonic seizures.
        - Valproic Acid & derivatives have been noted to increase the risk of myocarditis. Use with caution, balancing the risk of seizures with the potential risk of myocarditis. Monitor for increased clozapine toxicities (eg., myocarditis, neutropenia, CNS effects) if combined with valproate. Consider monitoring serum clozapine and/or norclozapine (N-desmethylclozapine) levels, as variable effects on the pharmacokinetics of clozapine have been reported with the combination.
        - Lamotrigine: Cannot be loaded. Slow titration to reduce risk of developing Steven-Johnson Syndrome. Good tolerability and limited weight gain. Effective for both generalized and myoclonic seizures.
        - Gabapentin: Effective in preventing generalized seizures but not myoclonic seizures.
        - Topiramate: Effective in preventing generalized seizures but not myoclonic seizures. Can cause weight loss but cognitive side effects can be problematic.
        - Levetiracetam: No interactions with clozapine.
        - Phenytoin and Carbamazepine: Both should be avoided as they will reduce clozapine plasma levels > 50%. Carbamazepine increases the risk of neutropenia.
    - Clozapine titration can be resumed after an anticonvulsant is added
      Of Note: 10% risk of generalized tonic-clonic seizures after four years; Risk is dose-dependent, doubling at 300-600 mg/day and tripling at > 600 mg/day
- Gastrointestinal monitoring:
    - Prevalence of constipation with clozapine: 32 – 60%
    - Monitor for constipation and treat prophylactically with:
        - High-fiber foods, adequate fluid intake, & exercise
        - Stool softeners: DSS 250 mg or Miralax 17 grams at initiation
        - Laxatives: Dulcolax 10 mg or Senna 17.2 mg daily
        - If constipation occurs prn lactulose
            - For non-responsive cases, start an intestinal secretagogue - lubiprostone or linaclotide)

Of Note: Paralytic ileus can occur if constipation not monitored and treated with fatality rate of 15 – 28%, compared to severe neutropenia fatality rate of only 2 – 4%

- Prevalence of hypersalivation with clozapine: 90% with greater severity at night
- Manage hypersalivation with anticholinergic medications or other treatments as needed
    - Anticholinergics: reduce drooling by 44%; however, long-term carries risk of dementia, falls, and mortality
    - First-line treatment:
        - Atropine 1% ophthalmic drops taken sublingually, initiate at 3 drops hs.
        - Terazosin 2 mg hs
        - Clonidine 0.1 – 0.2 mg hs
    - Second-line treatment:
        - Glycopyrrolate 2 mg hs – does not cross blood-brain barrier, reducing anticholinergic effect on cognitive functions observed in other anticholinergics. Still carries risk for constipation
    - Third-line treatment:
        - Botulinum Toxin-B injections into salivary glands

- Therapeutic drug monitoring:
    - Check levels during titration, in cases of poor response, or when non-adherence is suspected
    - Aim for 350-600 ng/mL, adjusting based on individual response and side effects
        - Average dose for TRS is ~400 mg/day
        - Check level in AM, approximately 8-10 hours after evening dose
        - Monitor clinical response for two weeks after reaching therapeutic level before further dosage increase
        - Reasonable to consider serum level > 350 ng/mL for refractory symptoms, although evidence of greater efficacy is limited
        - Variability in clozapine metabolism can lead to unpredictable levels making initial serum monitoring essential.
        - Continuous monitoring not mandated; however, beneficial in monitoring adherence
- Monitor smoking and caffeine intake due to their impact on clozapine metabolism
- Additionally, monitor for Neuroleptic Malignant Syndrome, hepatoxicity, pulmonary embolism, anticholinergic toxicity, and cognitive/motor performance.
- Continuously educate patients on adherence, side effects, and when to seek help

Missed Doses

- Client Education
    - Take the missed dose as soon as you remember.
    - If it is close to the time for your next dose, skip the missed dose and resume your regular dosing schedule.
    - Do not take two doses at the same time or extra doses.

        - If you miss one day or more of clozapine, you may need to restart at a lower dose to reduce the risk of side effects. Call your doctor to find out how to restart the medication.
        - It's important to take clozapine every day as prescribed to avoid increased side effects and relapse of symptoms.
- Reinitiation of treatment after interruption
    - Reinitiation after an interruption requires dosage reduction to minimize the risk of hypotension, bradycardia, & syncope
        - 1 day's missed dosing: Resume at 40% to 50% of the established dose
        - 2 days' missed dosing: Resume at approximately 25% of the established dose.
        - Longer interruptions: Re initiate at 12.5 mg once or twice daily.
    - If these dosages are well-tolerated, dosage may be increased to the previous dose more quickly than is recommended for initial treatment.
    - A clozapine to N-desmethylclozapine (norclozapine) ratio (CLZ:NDMC) greater than 2 is suggestive of a non-trough sample, a recent missed dose, or the saturation/inhibition of the CYP1A2 or other CYP450 enzymes.

Discontinuation:

- Taper clozapine gradually to minimize the risk of cholinergic rebound syndrome or rapid relapse
- Prescribe anticholinergic medications to prevent withdrawal symptoms, specifically Cholinergic Rebound Syndrome (nightmares, anxiety, insomnia, nausea, diarrhea, sweating, confusion, delirium, and/or catatonia)
    - For nonsmokers, for every 50 mg clozapine add 1 mg benztropine or 25 mg diphenhydramine.
    - For smokers, double the dose
    - Taper anticholinergics slowly after two weeks
- In cases of severe adverse effects (e.g., agranulocytosis, myocarditis), urgent discontinuation may be necessary

Documentation and Communication:

- Maintain detailed records of all monitoring parameters, interventions, and communication with healthcare providers
- Collaborate with other specialists (e.g., hematology, cardiology) as needed to manage adverse effects

By implementing this policy, healthcare providers can optimize clozapine therapy while minimizing the risk of serious adverse events, ultimately improving outcomes for patients with treatment-resistant schizophrenia and other indicated conditions.

Clinical Pearls, Clozapine Facts, and Resources

- Patients with TRS receiving clozapine treatment are more likely to maintain sobriety and reduce substance use compared to patients on other antipsychotics due to its effects on cravings

- MDs often prescribe more than two antipsychotics before using clozapine despite APA guidelines, and many psychiatrists do not use clozapine at all.
- Clozapine benefits vs risks:

Benefits	Risks
Treatment resistance (>60% will have a significant response	Early severe neutropenia (0.4%)
Decreases suicide risk five-fold	Myocarditis (0.18%)
Reduction in all-cause mortality by 45%	Seizures (predictor of good response)
Unique anti-aggression properties	Chronic sedation
Reduces substance misuse	Constipation
Greater functional ability	Drooling
Helps stop the "revolving door" of repeated emergency and acute psychiatric care	

- References for further information
  - SMI Adviser (an APA & SAMHSA initiative, free)
  - The Clozapine Handbook by Jonathan Meyer and Stephen Stahl
  - Clozapine 101 APA 2023
  - Managing Clozapine Side Effects APA 2023
  - Clozapine REMS
  - Clozapine Underutilization: Addressing the Barriers
- Lexicomp Online. Accessed 10 July 2024.
- Micromedex Online. Accessed 10 July 2024.
- Mayo Clinic. "Clozapine (Oral Route) Proper Use." Mayo Clinic, 1 July 2024, https://www.mayoclinic.org/drugs-supplements/clozapine-oral-route/proper-use/drg-20066859. Accessed 10 July 2024.
- NAMI. "Clozapine (Clozaril and Versacloz)." National Alliance on Mental Illness, last reviewed January 2024. https://www.nami.org/about-mental-illness/treatments/mental-health-medications/types-of-medication/clozapine-clozaril-and-versacloz/. Accessed 10 July 2024.

RECOMMENDED MONITORING FREQUENCY AND CLINICAL DECISIONS BY ANC LEVEL		
ANC Level	**Treatment Recommendation**	**ANC Monitoring**
Normal Range for a New Patient **GENERAL POPULATION** • ANC ≥ 1500/µL	• Initiate treatment • If treatment interrupted: - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient	• Weekly from initiation to six months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
BEN POPULATION • ANC ≥ 1000/µL • Obtain at least two baseline ANC levels before initiating treatment	• Discontinuation for reasons other than neutropenia	• See Section 2.4 of the full Prescribing Information
Mild Neutropenia (1000 - 1499/µL)*	**GENERAL POPULATION** • Continue treatment	**GENERAL POPULATION** • Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION • Mild Neutropenia is normal range for BEN population, continue treatment • Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	**BEN POPULATION** • Weekly from initiation to six months • Every 2 weeks from 6 to 12 months • Monthly after 12 months • See Section 2.4 of the full Prescribing Information
Moderate Neutropenia (500 - 999/µL)*	**GENERAL POPULATION** • Recommend hematology consultation • Interrupt treatment for suspected Clozapine induced neutropenia • Resume treatment once ANC normalizes to ≥ 1000/µL	**GENERAL POPULATION** • Daily until ANC ≥ 1000/µL, then • Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION • Recommend hematology consultation • Continue treatment	**BEN POPULATION** • Three times weekly until ANC ≥ 1000/µL or ≥ patient's known baseline. • Once ANC ≥ 1000/µL or patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
Severe Neutropenia (< 500/µL)*	**GENERAL POPULATION** • Recommend hematology consultation • Interrupt treatment for suspected Clozapine induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	**GENERAL POPULATION** • Daily until ANC ≥ 1000/µL • Three times weekly until ANC ≥ 1500/µL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µL
	BEN POPULATION • Recommend hematology consultation • Interrupt treatment for suspected Clozapine induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	**BEN POPULATION** • Daily until ANC ≥ 500/µL • Three times weekly until ANC ≥ patients established baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/µL or at patient's baseline

* Confirm all initial reports of ANC less than 1500/µL (ANC < 1000/µL for BEN patients) with a repeat ANC measurement within 24 hours

** If clinically appropriate