Clozapine in the Post-REMS Era: the Dust is Still Settling

Fred Jarskog, M.D.

Professor of Psychiatry

Director, North Carolina Psychiatric Research Center

UNC-Chapel Hill

Disclosures

Within the past 24 months:

- Research funding: Boehringer-Ingelheim, Otsuka, Click Therapeutics, Recognify, NIH
- Consulting: UpToDate
- Speaker fees: none
- Stock ownership: none

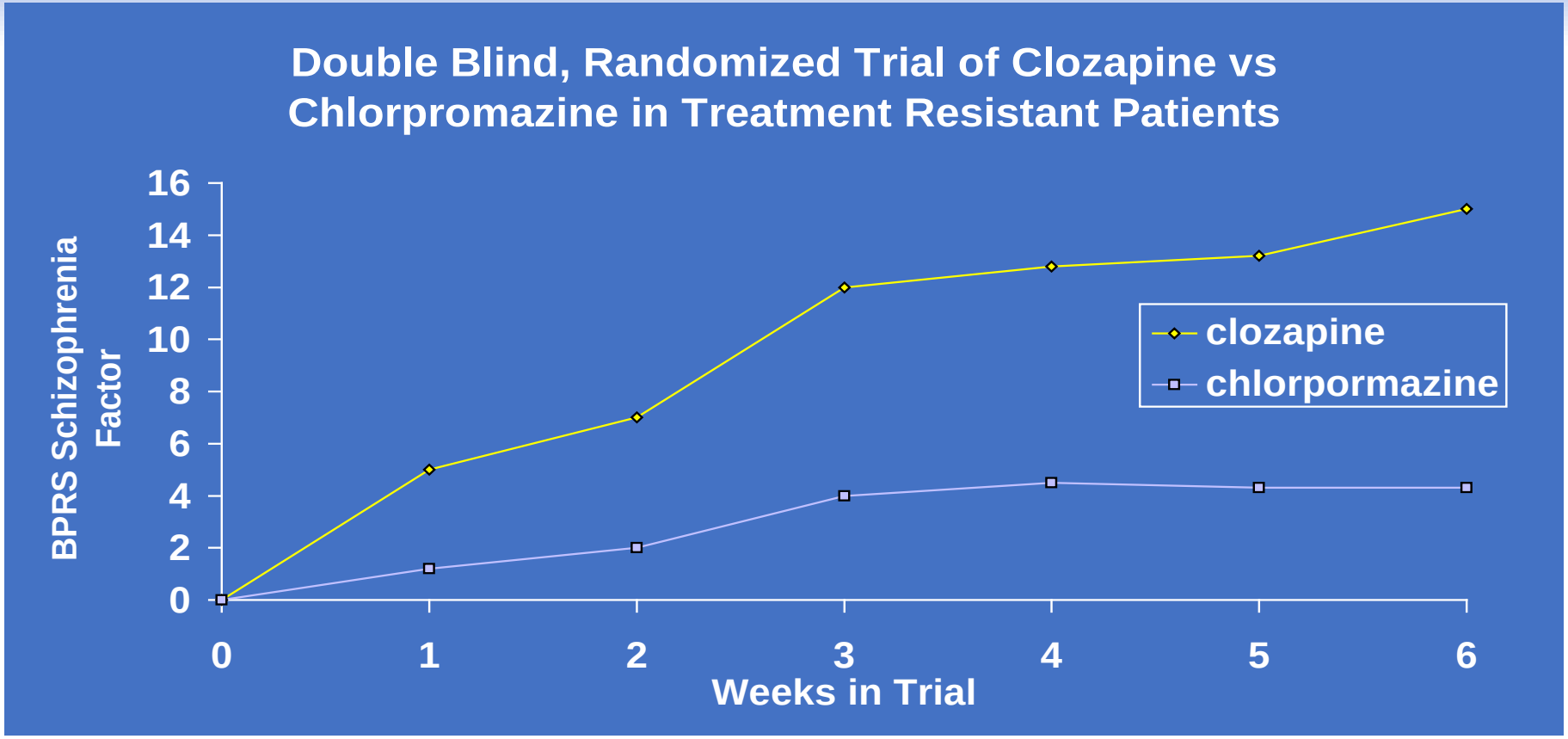
Outline

- **Clozapine indications**
- **Clinical benefits compared to other antipsychotics**
- **Use of clozapine**
  - Underutilization
  - REMS discontinuation
  - ANC monitoring for agranulocytosis in the post-REMS era
  - Additional side-effect assessment and management
  - Clozapine pharmacokinetics
  - North Carolina Clozapine Network (NCCN)

Clozapine – brief history

- Synthesized in 1959, studied for antipsychotic efficacy in Europe in 1960's. Efficacy was questioned due to *lack* of EPS
- First approved in 1972 in Austria and Switzerland
- In 1975, approved in Finland and within 4 months 16 patients had developed agranulocytosis, 8 of whom died
- Clozapine was subsequently withdrawn from all markets
- In 1988, a large study found clozapine superior to chlorpromazine for patients with treatment-resistant schizophrenia (30% response rate for CLOZ vs. 4% for CPZ) (Kane et al., 1988, Arch Gen Psychiatry)
- FDA-approval in 1989 with mandated WBC/ANC monitoring. In 2015, the FDA instituted a Risk Evaluation and Mitigation Strategies (REMS) program for clozapine

Clozapine vs Chlorpromazine in Treatment-Resistant Schizophrenia



Kane et al., 1988, Arch Gen Psychiatry

Clozapine Indications

FDA-approved indications:

- **Treatment-resistant schizophrenia**
- **Reduce suicidal behavior in people with schizophrenia or schizoaffective disorder**

Treatment-Resistant Schizophrenia: definition

- **Persistent psychotic symptoms of at least moderate severity, lasting at least 3 months**
- **At least moderate impairment in functioning**
- **≥2 adequate antipsychotic drug trials**
  - At least 2 different antipsychotic agents
  - Each of ≥6 weeks in duration at a therapeutic dose
  - Each agent dosed at ≥600 mg chlorpromazine equivalents per day or highest tolerated dose

Howes et al., 2017, AJP

Importance of Early Intervention with Clozapine in TRS

- **~30% of all people with schizophrenia have TRS**
- **In people who have TRS and are eligible for clozapine:**
  - Mean APD trials prior to clozapine = **5** (Taylor et al, J Clin Psychiatry, 2003)
  - Mean delay of **~4 years** prior to clozapine trial (Howes et, Br J Psychiatry, 2012)
    - Associated with antipsychotic polypharmacy in 36.2% and high-dose treatment in 34.2% of patients
- **A population-based register study in Denmark found an 8-11% reduction in likelihood to response to clozapine for *each* different APD trial prior to clozapine (Nielsen et al, J Clin Psychopharmacol 2012)**

Clozapine is recommended for TRS by leading schizophrenia treatment guidelines

- **Endorsed by many schizophrenia treatment guidelines, including:**
  - American Psychiatric Association (2021, APA)
  - Schizophrenia Patient Outcomes Research Team (PORT) (Buchanan et al, 2010, Schizophr Bull)
  - National Institute for Health and Care Excellence (NICE) clinical guideline for schizophrenia
  - World Federation of Societies of Biological Psychiatry (Hasan et al, 2012, World J Biol Psychiatry)
  - Royal Australian and New Zealand College of Psychiatrists (Galletly et al,2016, Aust NZ J Psychiatry)

Clozapine and Suicide

- International Suicide Prevention Trial (InterSePT)
  - 2-year trial of 980 people with schizophrenia or schizoaffective d/o randomized to clozapine or olanzapine showed significant reductions for clozapine on:
    - Suicidal behavior (0.76 HR, p=.03)
    - Attempted suicides (34 vs 55, p=.03)
    - Required hospitalizations (82 vs 107, p=.05)

(Meltzer et al., 2003, Arch Gen Psychiatry; 60:82-91)

- Meta-analysis of long-term studies focused on suicide (n=240,564) found:

2.9-fold reduction

in completed suicides for treatment with clozapine compared to treatment with other antipsychotics.

(Hennen and Baldessarini, 2005, Schizophr Res; 73:139-145)

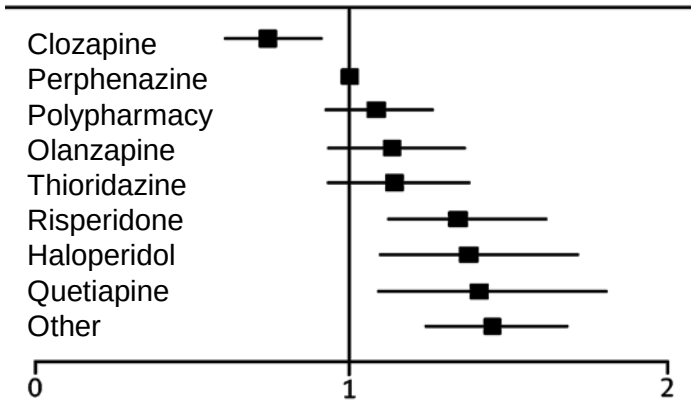
Clozapine and Violence

- **Within-subject study in people with chronic psychotic disorders in Sweden using linked prescription, hospitalization and sociodemographic registers.**
- **Primary outcome: violent offenses occurring before and after clozapine (n=1,004) or olanzapine (n=2,256) initiation.**
- **Adjusted rate reduction of violent offenses for treatment compared to before treatment was 87% for clozapine and 8% for olanzapine.**

Bhavsar et al., 2020, Schizophr Bull

Clozapine and Mortality

- Fin11 study: 11 yr population cohort study of N=66,881 people with SCZ



(Tiihonen et al., 2009, Lancet)

- Meta-analysis of 24 studies reporting on 1,327 deaths from any cause in 217,691 pt yrs for individuals treated with clozapine showed:

Mortality rate = 6.7 per 1,000 patient yrs

Mortality rate ratio = 0.56 (p=.007)

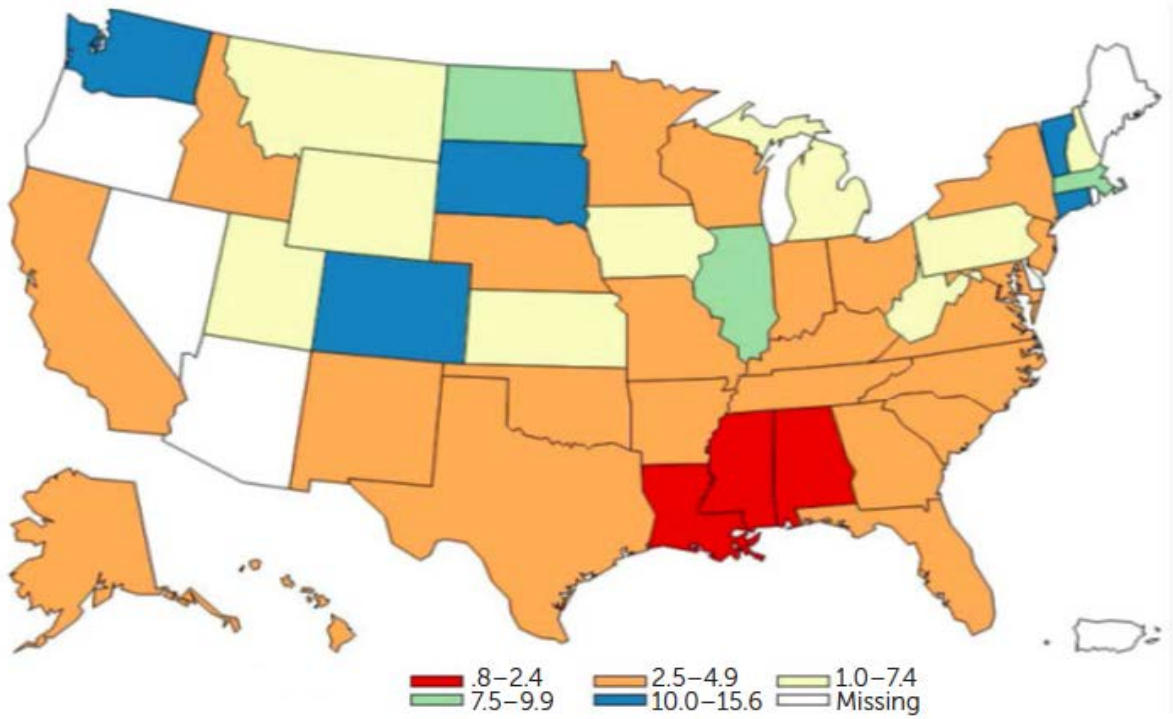
in patients treated continuously with clozapine compared to other antipsychotic medications

(Vermeulen et al., 2019, Schizophr Bull)

Clozapine underutilization

Mean national clozapine prescribing rate = 4.8%

FIGURE 1. Clozapine prescribing rates among Medicaid-insured adults with schizophrenia, 2006–2009



Olfson et al, Psychiatric Serv. 2016; 67:152

Clozapine neutrophil (ANC) monitoring

Current FDA recommendation since REMS discontinuation:

No change from pre-REMS recommendations

ANC	Treatment Recommendations	ANC Monitoring
New patient initiation ANC ≥1500/mm^3	Initiate treatment	Weekly x6 months Every 2 weeks 6-12 months Monthly after 12 months
Mild Neutropenia ANC 1000-1499/mm^3	Continue treatment	Redraw to confirm 3X weekly until ANC ≥1500 Then return to patient's last normal range monitoring interval
Moderate Neutropenia ANC 500-999/mm^3	Recommend hematology consult Interrupt treatment Resume once ANC normalizes to at least 1000	Redraw to confirm Daily ANC until at least 1000 Then three times weekly until at least 1500 Once ANC at least 1500, check weekly for 4 weeks then return to normal interval
Severe Neutropenia ANC <500/mm^3	Recommend heme consult Interrupt treatment Do not rechallenge unless benefits outweigh risks	Redraw to confirm Daily ANC until at least 1000 Then three times weekly until at least 1500 If rechallenged, resume as a new patient

Benign Ethnic Neutropenia (BEN)

- BEN represents persistent mild neutropenia (1,000≤ANC<1,500 cells/mm^3) in persons with no h/o recurrent or unusual infections
- BEN occurs commonly (25-40%) in people of African and Middle Eastern descent. Linked to allelic variant of Duffy (FY) Antigen for Receptor Chemokine *(DARC)* Gene. 33% of individuals with Duffy null genotype meet "neutropenia" criteria (Reich et al, 2009, PLOS Genetics)
- BEN may account for some of the racial disparities that have been identified in clozapine treatment. The frequency of clozapine treatment has been found to be lower in Black patients and this group is 2x as likely to have clozapine discontinued d/t ANC falling below REMS monitoring thresholds (Kelly et al, 2006, J Clin Psychiatry; Kelly et al, 2007, Schizophr Bull)
- In some cases it may be necessary to involve a hematologist to determine BEN status, but usually BEN can be established by a non-specialist by reviewing historical ANC values (National Assoc State Mental Health Program Directors, Clozapine White Paper, 2016)

Clozapine ANC monitoring guidelines for patients with BEN

ANC	Treatment Recommendations	ANC Monitoring
New patient initiation ANC ≥1000/mm^3	Obtain at least two baseline ANC before initiation Initiate treatment	Weekly x6 months Every 2 weeks 6-12 months Monthly after 12 months
Mild Neutropenia ANC 1000-1499/mm^3	Continue treatment Mild neutropenia normal range for BEN	Weekly x6 months Every 2 weeks from 6-12 months Monthly after 12 months
Moderate Neutropenia ANC 500-999/mm^3	Recommend hematology consult Continue treatment	ANC three times weekly until at least 1000 or pt's known baseline Then check weekly for 4 weeks then return to patient's normal range interval
Severe Neutropenia ANC <500/mm^3	Recommend heme consult Interrupt treatment Do not rechallenge unless benefits outweigh risks	Daily ANC until at least 500 Then three times weekly until at least to pt's normal baseline If rechallenged, resume as a new patient

Clozapine-associated neutropenia

- **Neutropenia**
  - **Severe neutropenia (a.k.a. agranulocytosis) – ANC <500 cells/mm^3**
    - Incidence: ~0.7% (Myles et al., 2018, Acta Psychiatr Scand)
    - Not dose dependent
    - Risk peaks by 4 weeks from clozapine initiation, ~85% of cases occur within 18 weeks, ~90% of cases occur within 1 year
    - Mortality: 0.02% (~1:5,000)
    - Case fatality rate: 2.8%
  - **Neutropenia – ANC <1,500 cells/mm^3**
    - Incidence: 3.9% (Myles et al., 2018, Acta Psychiatr Scand)
    - Risk peaks within 6-18 weeks (Munro et al., 1999, Br J Psychiatry)
    - 75% of people who develop mild neutropenia will not progress to moderate or severe neutropenia

Risk of minor vs severe clozapine-associated neutropenia in Australia and New Zealand: retrospective cohort study (n=26,630)

- Largest and longest cohort study to date
- Serious neutropenia – 0.9% (18 wks), 1.4% (104 wks)
- Minor neutropenia - 1.7% (18 wks), 3.7% (104 wks)
- 18.9% of patients w/ serious neutropenia had prior minor neutropenic event. However, having minor neutropenic event did not predict serious neutropenia

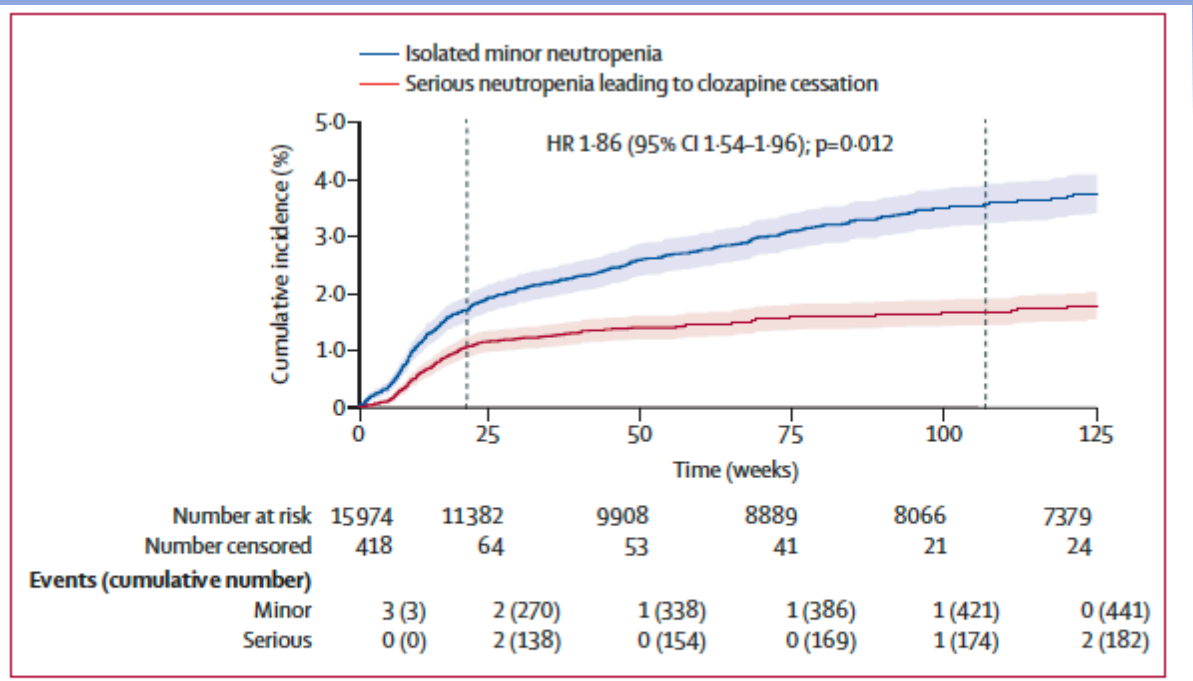


Figure 1: **Competing risks survival analysis of neutropenic events in patients with no previous clozapine exposure (n=15 973)**

Lines show Cox proportional HR and shaded areas show 95% CI. Vertical dotted lines are at 18 weeks and 2 years. Number at risk and censoring events are in the appendix (pp 8–14). HR=hazard ratio.

Australia/New Zealand cohort study conclusions

- **Following a 2 year period of ANC monitoring for CLZ tx, a patient with no serious neutropenic event could safely discontinue ANC monitoring**
- **After 2 years of cumulative monitoring, ANC monitoring may not need to be restarted after a treatment interruption given that previous CLZ exposure appears to be protective for future serious neutropenia**
- **Only 36% of minor neutropenia occur within 18 wks, with a linear cumulative incidence thereafter. Minor neutropenia during CLZ exposure is unlikely to be of clinical relevance**
- **Point prevalence of idiopathic moderate neutropenia (ANC<1.0×10^9 cells/L) is ~1.4% in general population. Therefore, it is likely that many late serious neutropenic events during CLZ tx reflect observation bias rather than event of clinical relevance. Continued monitoring after 2 yrs of CLZ tx is likely to lead to unnecessary cessation of CLZ d/t either a minor neutropenic event or a non-causally related severe neutropenic event.**

European Clozapine Task Force: Joint expert statement on clozapine blood monitoring

- Group of clinical and research psychiatrists and pharmacologists with schizophrenia expertise from 18 countries under European Medicines Agency (EMA) regulation (Verdoux et al., 2025 European Psychiatry)

Recommended Clozapine ANC monitoring schedule:

Yr 1:	ANC weekly for 18 weeks, then q4 wks for 34 wks
Yr 2:	ANC q12 wks if no h/o neutropenia during Yr 1
After Yr 2:	ANC yearly if no neutropenia during yrs 1 and 2

Standard threshold for initiation/continuation	ANC$\geq$1.5k cells/mm^3
Twice weekly monitoring	ANC 1.0-1.5k cells/mm^3
Discontinuation	ANC <1.0k cells/mm^3

July 2025: European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee recommended and adopted new guidelines

Global Delphi consensus guidelines for clozapine ANC monitoring

- **Weekly ANC for the first 18 weeks of clozapine treatment**
- **Q4wk ANC from 18 weeks through end of 24 months**
- **Annual ANC monitoring thereafter**

  - ANC threshold: <1.0 cells/mm^3 (<0.5 cells/mm^3 BEN, DARC null)
  - If ANC below threshold and no probable cause, consider ceasing clozapine according to clinical judgement
  - After 2 yeas of treatment, strongly consider alternative causes before clozapine cessation

Siskind et al., 2025, Lancet Psychiatry

ANC monitoring in the U.S. moving forward

- FDA recommends continuing the approved indefinite ANC monitoring as described in the clozapine product insert
- The FDA is planning modifications to the package insert to be consistent with REMS removal but it appears unlikely that this will include specific changes to the ANC monitoring schedule
- Endorsement of a modified ANC monitoring schedule by a national professional association such as the American Psychiatric Association could provide a straightforward mechanism for general adoption of a new schedule, but the if and when of such an endorsement is currently uncertain
- General consensus across all studies on importance of weekly ANC for first 18 wks of clozapine tx.
- Avoid instituting new barriers to clozapine use
- Educate patients, families and providers
- General recommendation to utilize a shared-decision making process with patients in terms of considering risks and benefits (Meyer and Rubio, 2025, J Clin Psychiatry)
- There is strong interest among advocacy organizations, consumers, researchers and practitioners to for consensus guidelines to be established, the exact process for this to occur remains uncertain

Clozapine side effects beyond agranulocytosis

- **Myocarditis**
  - Incidence: Up to 3% (Ronaldson et al, 2015, Acta Psychiatr Scand)
  - Highest risk during first 4 weeks of treatment, risk tapers sharply by 8 weeks of treatment

  Recommended screening

    - Obtain ECG at baseline (Knoph et al, 2018, Schizophr Res)
    - Myocarditis ROS: chest pain, weakness, dyspnea, peripheral edema, fever, palpitations/tachycardia
    - Educate patient/family about these symptoms
    - Obtain cardiac panel at baseline and weekly for 4 weeks (troponin I, CRP, CK, CK-MB, pro-BNP), may continue beyond 4 weeks for clinical concerns.
      - Troponin I is most sensitive, but elevation in one or more measures together with physical symptoms should raise concern
      - Based on large case series, troponin I $\geq$2x ULN or CRP >100 mg/L was highly sensitive for symptomatic myocarditis (Ronaldson et al., 2011)
  - **Evidence for myocarditis usually requires clozapine discontinuation**

Clozapine side effects

- **Cardiomyopathy**
  - Incidence: 0.02-0.1% (Layland et al, 2009, Med J Austral)
  - Insidious onset, usually >6 months after initiation
  - May be asymptomatic or associated with signs/sxs of heart failure
  - May have been preceded by subclinical myocarditis
  - Many possible causes, not just clozapine

Clozapine side effects

- **Seizures**
  - Risk is dose-related, ~1% in doses up to 300 mg/day
  - Risk increases to ~3% at 600 mg/day
  - Clozapine seizures are sometimes heralded by myoclonic jerks -> add anticonvulsant
  - Consider adding anticonvulsant (eg lamotrigine or VPA) for clozapine ≥600 mg/day for seizure prophylaxis
- **DVT/Pulmonary Embolus**
  - Rare but associated with high mortality rate
- **Eosinophilia (>500 cells/mm^3)**
  - Incidence ~1%, may be benign but can signal subclinical myocarditis or other end-organ inflammatory process (eg nephritis, pancreatitis, hepatitis) (Roberts et al, 2011, Am J Psychiatry)
  - Recommend hematology consult for EOS >1,500 cells/mm^3

Clozapine side effects

- **Constipation**
  - Clozapine is highly anticholinergic
  - Constipation occurs early and is a common side effect
  - In severe cases, can represent a medical emergency when associated with paralytic ileus and/or intestinal perforations
  - Encourage adding more fruits, legumes, whole grain foods to diet
  - Treat constipation early and aggressively – osmotic (e.g. polyethylene glycol) and stimulant (e.g. bisacodyl) laxatives, bulking agents (e.g. Metamucil), stool softeners (e.g. docusate)

Clozapine side effects

- **Orthostatic hypotension**
  - Mild/moderate is common during titration phase, typically improves with time
  - Management strategies include slowing rate of titration, shift dosing to HS only, encourage hydration, advise slow/careful rising from horizontal or sitting positions
  - Rarely, clozapine is associated with severe orthostasis, bradycardia and syncope
  - Benzodiazepine co-administration may exacerbate hypotension. Avoid starting a patient already taking benzodiazepine as this has been associated with circulatory collapse (FDA package insert)
  - Under certain circumstances, use of midodrine (α_1 agonist approved for symptomatic orthostatic hypotension) may be considered, however this should not be used routinely and would only initiate in consultation with primary care/internal medicine provider

Clozapine side effects

- **Cardiometabolic side effects**
  - **Weight Gain**
    - Clozapine has a high risk for causing weight gain
    - Educate patients on importance of eating healthy diet and increasing physical activity
    - Body weight should be checked at each outpatient visit - track weight and BMI. Weight gain of 5% over baseline within 1 month predicts 15% weight gain by 3 months (Vandenberghe et al, 2015, J Clin Psychiatry)
    - Evidence-based pharmacological approaches for achieving modest weight loss while taking APD include adjunctive metformin (best evidence), topiramate and aripiprazole (Mizuno et al, 2014, Schizophr Bull)
    - Use of GLP1 agonists is becoming much more common, evidence base for use in this setting has been limited until very recently (Ganeshalingam et al., 2025, JAMA Psychiatry)

Monitoring for cardiometabolic side effects for antipsychotic medication treatment

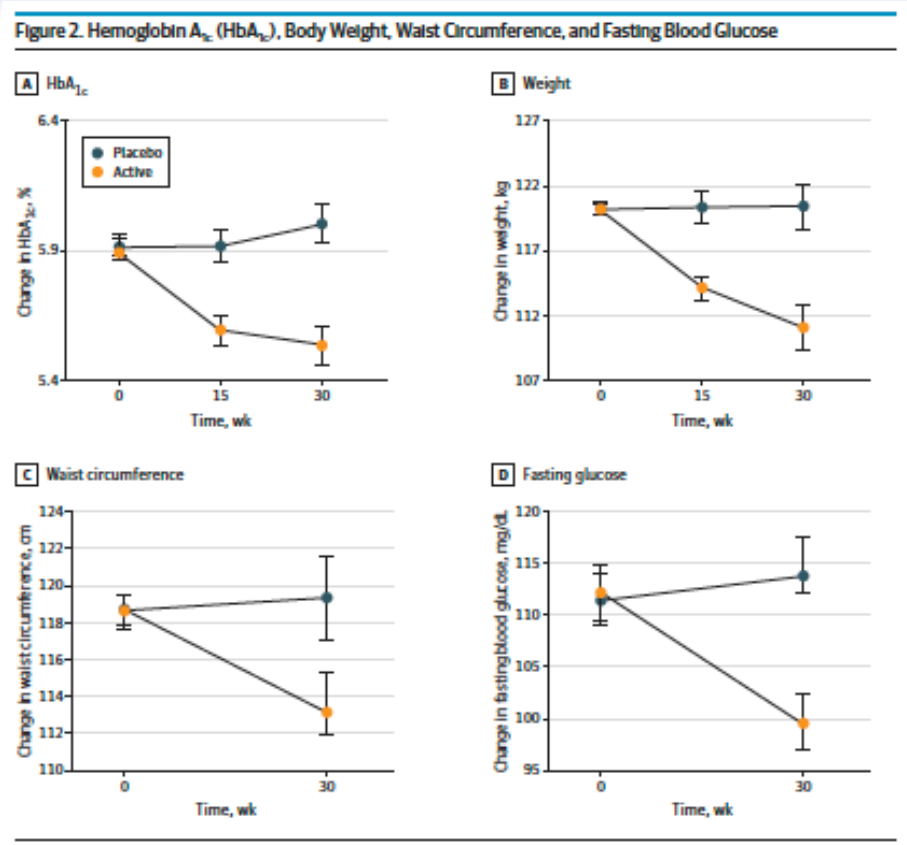
Risk factor	Timing of assessment					
	Baseline	6 weeks	3 months	12 months	Ongoing Monitoring	
					Quarterly[f]	Annually[f]
Personal and family history of diabetes, hypertension, or CVD	X					X
Smoking status, physical activity, diet	X	X	X		X	
Weight, BMI	X	X	X		X	
Blood pressure	X	X	X		X	
Fasting glucose or HbA1c	X		X	X		X
Lipid profile (fasting or non-fasting)	X		X	X		X

Adapted from De Hert et al., 2012, Nature Reviews Endocrinology

Consistent with 2021 APA Schizophrenia Treatment Guidelines

Semaglutide for SGA-associated weight gain

30 wk RCT in 154 SGA-treated patients with prediabetes and overweight/obesity, differential weight loss for semaglutide vs placebo was 9.2 kg (20.2 lbs)



(Ganeshalingam et al., 2025, JAMA Psychiatry)

Clozapine side effects

- **Cardiometabolic side effects**
  - **Diabetes**
    - Clozapine – and all antipsychotic drugs – are associated with insulin resistance which appears to be related both to the effects of weight gain and both central (hypothalamic) and peripheral (pancreatic) effects of D2 antagonists (Freyberg et al, 2017, Front Neurosci)
    - Prevalence of diabetes in schizophrenia is up to 2X higher than the general population (16-25%, Chwastiak et al, 2015 Lancet; Lambert et al., 2023 BMC Open Diabetes Research & Care; Huo et al. 2021, J Psychiatric Res)
    - Obtain baseline HbA1C, then at least yearly. More frequent if abnormal (pre-diabetic range) and ensure that patient has a PCP
  - **Hyperlipidemia**
    - Risk is shared with all APDs
    - Obtain baseline lipid panel, then at least yearly, more frequent if abnormal. Refer to PCP for management

Clozapine side effects

- **Sedation**
  - Common, often improves with time. Options including switching clozapine dose to HS, consider modest dose reduction, some may benefit from AM caffeine intake.
  - Can consider modafinil (50-200 mg per day) in severe cases (not an FDA-approved indication). Would only consider modafinil for patients who have demonstrated good clinical improvement on clozapine given potential risks of psychotic exacerbation and misuse.
- **Sialorrhea**
  - Common, usually worse at night, may benefit from anticholinergic agents such as ipratropium bromide 1-2 sprays sl or 1% atropine ophthalmic drops 1-2 drops sl. Glycopyrrolate 1-2 mg per day is less likely to add central anticholinergic effects and may be effective (Man et al., 2017, J Clin Psychopharmacol).
- **Tachycardia**
  - Common, often improves with time, can add low dose beta-antagonist. Cardioselective (β_1) agent is preferable, e.g. metoprolol 12.5-25 mg qday. Non-selective (β_1 and β_2) agent such as propranolol 10-20 mg bid is a reasonable alternative if cardioselective agent leads to hypotension or is not effective.

Clozapine pharmacokinetic interactions

- **Clozapine is metabolized primarily by CYP1A2**
  - Lesser contributions from CYP3A4, CYP2D6, CYP2C19
- **Strong CYP1A2 inhibitors can lead to clozapine toxicity at usual doses**
  - Fluvoxamine, ciprofloxacin
- **Weak/moderate CYP1A2 inhibitors may increase clozapine levels**
  - Caffeine, oral contraceptives
- **CYP1A2 inducers can substantially lower clozapine levels and require increased dosing**
  - Tobacco smoking

North Carolina Clozapine Network (NCCN): Expanding Clozapine Use in NC

- NCCN is part of the Center for Excellence in Community Mental Health, Dept of Psychiatry at UNC-Chapel Hill
- NCCN provides free consultation to providers in the community with clozapine-related questions
- Supported by UNC experts in clozapine use (Drs. Fred Jarskog and John Gilmore), cardiology (Dr. Brian Jensen), hematology (Dr. Stephen Moll) as well as pharmacy and nursing
- **Access to NCCN is available by contacting Dr. Fred Jarskog**

  Email: Jarskog@med.unc.edu Phone: 919-843-7683