THE CRUCIAL CASE FOR CLOZAPINE AND ENSURING SUCCESSFUL TRIALS

BRIEF CLINICAL UPDATES

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Clozapine

All relevant financial relationships have been mitigated.

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CLOZAPINE BENEFITS

- Only medication approved for treatment resistant schizophrenia
- FDA approved for reduction of suicidality and suicidal behavior
- Superiority over other antipsychotics
- Reduction in all-cause mortality
- Lower all-cause discontinuation rates compared to other agents
- Lowest risk of tardive dyskinesia and may improve AIMS scores
- Improvement of treatment adherence
- Improvement in quality of life and function

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CLOZAPINE

HARMS AND BARRIERS FROM A “NO BLOOD, NO DRUG“ PHILOSOPHY

- REMS relaunch in 2021 caused patient harms
- Elimination of REMS - February 24, 2025: the “FDA has determined that the REMS program for clozapine is no longer necessary to ensure the benefits of the medicine outweigh that risk”
  - No registration for prescribers, patients, pharmacies
  - No reporting of ANCs
  - Mitigate issues that went above REMS requirements (faxing labs)

Clozapine REMS. 2015. https://www.fda.gov/drugs/

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CLOZAPINE

NEUTROPENIA

- Estimated incidence of neutropenia
  - Severe neutropenia 0.9%
  - Fatal neutropenia 0.013%
- Risk of severe neutropenia decreases over time
  - <18 weeks: 6.76/1,000 patient-years
  - Months 6-12: 0.7/1,000 patient-years
  - Months >12: 0.39/1,000 patient-years
- What does this mean for monitoring…
  - Expert consensus statement is forthcoming
    - *weekly: 18 weeks, monthly: 1-2 years, then annually or as clinically indicated?*
  - FDA still recommends that prescribers monitor patients' ANC according to the monitoring frequencies described in the prescribing information

Schulte PFJ. 2006;40(4):683-8.; Griffith RW, Saameli K, 1975; 7936: 657
Myles N, et al. 2018: 138: 101–109; https://www.clozapinepluswerkgroep.nl/

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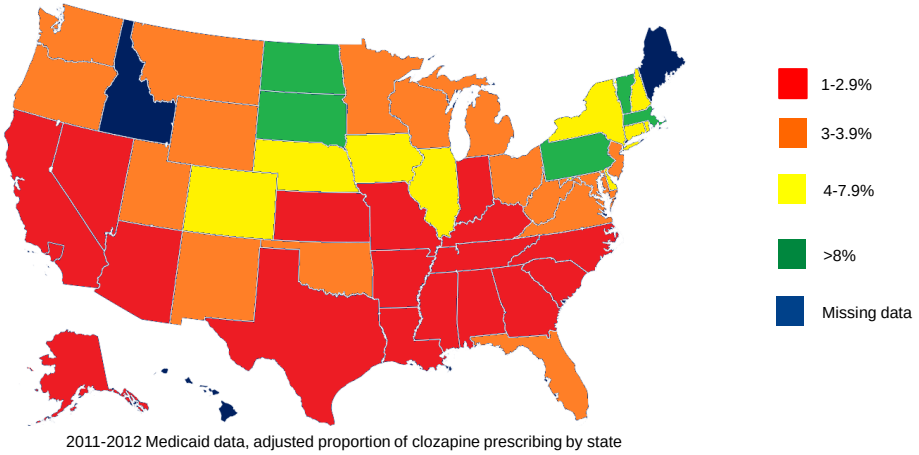
CLOZAPINE

UNDERUTILIZATION AND BARRIERS: A LIFE-OR-DEATH MATTER

https://www.youtube.com/watch?v=8GqWDQ8nicA



2011-2012 Medicaid data, adjusted proportion of clozapine prescribing by state

Figure adapted from supplemental material: Psychiatr Serv. 2022;73(5):492-500.

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THE CONCERN WITH CLOZAPINE DELAYS

- Each new antipsychotic trial reduces the likelihood of response by ~10%
- Each hospitalization reduces the chance of response by ~5%
- Delayed initiation is associated with greater risk of discontinuation
- Yoshimura B, et al.
  - For a delay ≤ 2.8 years (median delay 0.8 years) the response rate was 81.6%
  - For a delay > 2.8 years (median delay 7.0 years), the response rate was 30.8%

Nielsen J, et al. J Clin Psychopharmacol. 2012;32:678-683; Yoshimura B, et al. Psychiatry Res. 2017;250:65-70; Üçok A, et al. Int Clin Psychopharmacol. 2015;30:290-295.

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ADDRESSING BARRIERS

- Example barriers that still exist
  - Hematologic monitoring
  - Adverse effects
  - Resource availability (laboratories, appropriate follow-up, etc)
  - Knowledge gaps
- Removing barriers
  - Quality improvement projects
  - Building supportive, multidisciplinary infrastructure
  - Implementing technologies (POC/rapid hematologic and TDM monitoring)
  - Education
  - Research

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EXAMPLE INITIATIVES AT MAYO

- Clozapine clinic with finger stick capillary collection of CBCs
- Transition of care monitoring with inpatient medical hospitalization
  - Ensure adherence and appropriate retitration when applicable
- Evaluation and improvement of clozapine level turnaround time
- Implementation of an inflammatory/myocarditis screening protocol
- Patient education center development patient education on clozapine and self-monitoring
- Evaluation of inflammatory markers and concentration-to-dose ratios
- Evaluation of bowel regimens, use, and access

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CLOZAPINE

ESCAPING THE LONG SHADOW OF NEUTROPENIA

- Where is the literature is evolving and the package insert is lacking
  - Inflammation/CRP monitoring
  - Titration rate and influence of inflammation and genetic ancestry on dosing
  - Pneumonia

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CLOZAPINE

A PRO-INFLAMMATORY MOLECULE

- Clozapine mediates macrophage/lymphocyte release of pro-inflammatory markers such as IL-6 and TNF-alpha
  - Occurs early after exposure
  - Increase increased with “rapid” or continued titration
  - Impact may be greater in women
  - Thinking beyond myocarditis
    - Isolated fever, isolated eosinophilia, myocarditis, hepatitis, colitis, acute interstitial nephritis, etc.
- Acute inflammatory processes impact the cytochrome P450 (CYP) system
  - ↓ CYP1A2 , ↓ CYP2C19, ↓ CYP3A4, ↔ CYP2D6
  - Clozapine levels dramatically rise in the setting of acute inflammation

Yuan X, et al. [published online ahead of print, 2022 Jan 26]. 2022; Røge R, et al. 2012;140(1-3):204-213. Maes M et al. 1997;26(2-3):221-225. Pollmächer T, et al. 1996;16(5):403-409

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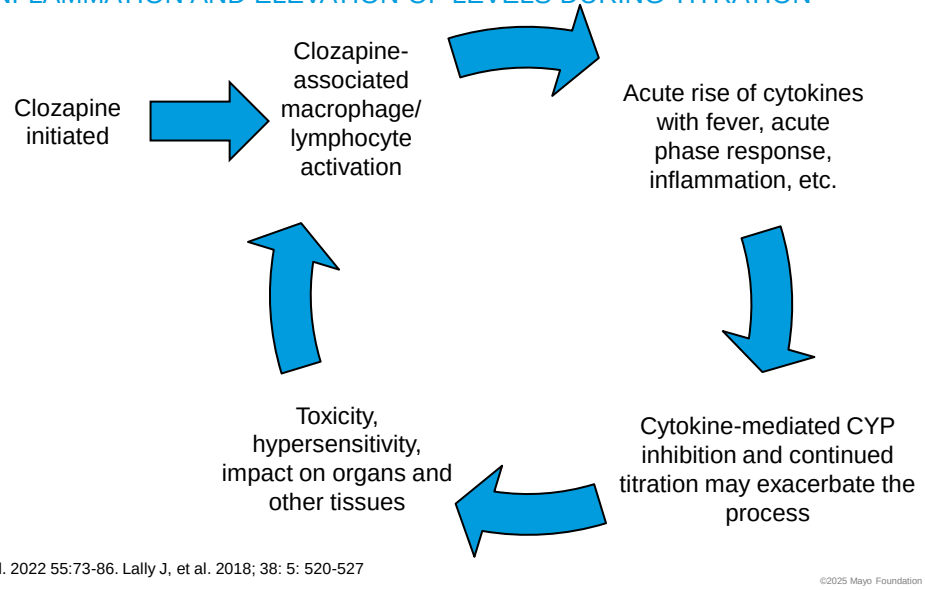
CLOZAPINE

INFLAMMATION AND ELEVATION OF LEVELS DURING TITRATION



de Leon J, et al. 2022 55:73-86. Lally J, et al. 2018; 38: 5: 520-527

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CASE EXAMPLE

INFLAMMATION AND ELEVATION OF LEVELS DURING TITRATION

- A 23-year-old, White, non-smoking female was started on clozapine
  - 12.5 mg for 1 day, increasing to 25 mg on day 2
  - Clozapine increased by 25 mg daily
- Once reaching 125 mg the patient reported intolerable sedation and dizziness
  - Clozapine level (non-steady-state): 278 ng/mL, CRP: 18 mg/dL (baseline <5 mg/dL), Troponin: undetectable
- C/D ratio of 2.2, representing decreased metabolism likely due to acute inflammation (ref: ~0.6-1.2 for patients of European ancestry)
- Dose reduced to 100 mg and slower titration commenced to 250 mg resulting in a level of 327 ng/mL (C/D ratio 1.3) as CRP trended back to near baseline

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CASE EXAMPLE

INFLAMMATION AND ELEVATION OF LEVELS DURING TITRATION

› Pharmacopsychiatry. 2022 Mar;55(2):73-86. doi: 10.1055/a-1625-6388. Epub 2021 Dec 15.

An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry–Based Personalized Dosing Titrations, CRP, and Clozapine Levels

- Recommendations on screening for inflammation (inpatient setting):
  - Baseline and weekly CRP monitoring for at least 4 weeks to detect **any** inflammation
  - Pause clozapine titration or lower the dose in the setting of inflammation
  - Use therapeutic drug monitoring weekly when possible
  - *"In countries with enough resources, adding weekly troponin during the first weeks appears reasonable."*
- Other protocols or expert opinion suggest monitoring for the first 4 to 8 weeks

de Leon J, et al. 2022 55:73-86. Correll CU, et al. 2022; 36: 659-79.
NSW Health. https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2022_011.pdf

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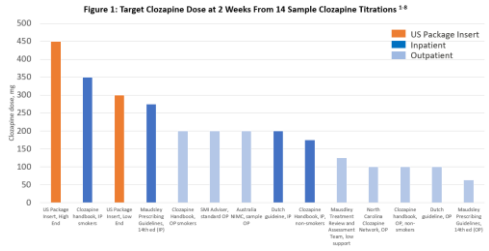
CASE EXAMPLE

INFLAMMATION AND ELEVATION OF LEVELS DURING TITRATION

- Early inflammatory response to clozapine has implications on titration
  - No studies have quantified what degree of elevation might be significant
  - Any CRP change from baseline may be important
- "Standard" titration is too rapid for some patients
  - Several studies have demonstrated that faster titration is associated with increased inflammatory response to clozapine



Cotes R. Are slow titrations safer than fast ones? Poster presentation at Schizophrenia International Research Society, 2023

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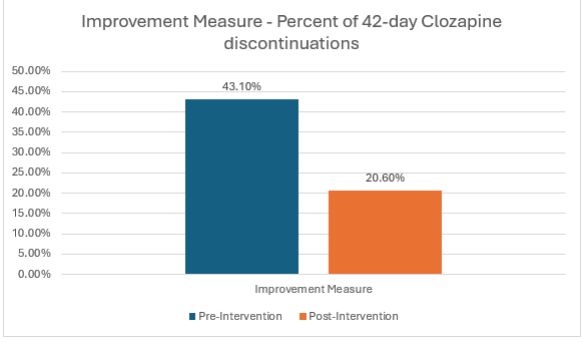
QI PROJECT: PROTOCOL IMPLEMENTATION

- Prior published study from Mayo data identified high early discontinuation rates
  - Goal of QIP was implementation of a strategy to improve discontinuation rates
- Implementation of an inflammation monitoring protocol was the strategy selected to evaluate 42-day discontinuation rates



Post-intervention (n=34):

- 2 myocarditis and 2 pericarditis
- 2 non cardiac/infection related fevers
- 1 isolated eosinophilia
- 8 cardiology consults, 10 echos, 2 medical transfers
- 1 case with significant CRP/troponin elevation deemed not myocarditis/pericarditis allowing for restart with slow titration
- 1 asymptomatic case of myocarditis
- Rate of new clozapine starts not negatively impacted, pre-/post-intervention 2.9% vs 4.2%

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INPATIENT SCREENING RECOMMENDATIONS

	Baseline	Day 7	Day 14	Day 21	Day 28	Week 5	Week 6**	Week 12-16	Annual
Mayo Inpatient Monitoring	CRP, troponin BNP + Current standard*: CBC, CMP, lipids, ECG	CRP, troponin, (level)	CRP, troponin, (level)	CRP, troponin, (level)	CRP, troponin, (level) ECG	CRP, troponin, (level)	CRP, troponin, (level)	Lipids, A1c	ECG, BNP (echo if +)

- Developed in collaboration with psychiatry, cardiology, and pharmacy departments
- Adopted by inpatient teams

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Baseline Screening	
• CRP < 10 mg/dL and troponin WNL	• Continue with weekly CRP and troponin monitoring • Titration per usual • Consider slower titration for patients of Asian ancestry, women, older patients, pediatric patients, and with interacting medications (e.g., estrogen containing oral contraception or valproate)
• CRP or troponin are not WNL	• If baseline CRP is >10 mg/dL consider slower titration • If baseline CRP is markedly elevated use clinical judgement whether to start clozapine until further work-up explaining inflammation is completed or initiate at a lower dose with slower titration, and consider trending CRP more frequently than weekly • If troponin elevated at baseline: consult cardiology unless clinical scenario warrants more urgent attention
Weekly Monitoring *	
• CRP < 10 mg/dL and normal troponin value	• Continue with weekly CRP and troponin monitoring for 6 weeks with usual titration • Consider clozapine level once reaching 200 to 300 mg (sooner in the setting of interacting medications, patients of Asian ancestry, with factors expected to reduce clozapine clearance, or tolerability concerns)
• CRP increases by 5 mg/dL and absolute value is over 10 mg/dL but no change in tolerability and normal troponin value	• If still titrating dose: reduce titration rate, continuing monitoring, consider trending CRP more frequently than weekly • If at target dose: continue monitoring, consider trending CRP more frequently than weekly • Consider clozapine level prior to reaching target dose
• CRP increases by 5 mg/dL and absolute value is over 10 mg/dL in conjunction with poor tolerability or dose to side effect mismatch and normal troponin value	• If still titrating dose: maintain current dose or consider dose decreasing based on severity of presentation and degree of CRP change until CRP normalizes, plateaus, or tolerability improves • Use clinical judgement regarding trending CRP or additional medical work-up for inflammation, as applicable
• Troponemia of <50 ng/L with no significant change at 3 hours, no symptoms, no CRP elevation	• Maintain current dose or reduce dose • ECG, TTE, cardiology consult, daily troponin • Consider resuming a slower titration with decreasing or normalizing troponin values
• All other scenarios ○ CRP elevation with asymptomatic troponemia ○ Troponemia <50 ng/L with concerning symptoms ○ Troponemia <50 ng/L with significant change at 3 hours ○ Troponin >50 ng/L	• Pause clozapine administration • ECG, TTE, cardiology consult, daily troponin • Discuss clozapine dosing or restart with cardiology

* Troponin testing referenced: 5th generation troponin T (i.e., high-sensitivity cardiac troponin assay); used with permission

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CLOZAPINE AND ANCESTRY

- Patient specific parameters to consider for titration and final target dose
  - Asian patients may have decreased metabolism
  - Black/African American patients may have increased metabolism
  - Females have decreased metabolism
  - Obesity may decrease metabolism
  - Drug interactions:
    - Inhibitors: Ciprofloxacin, fluvoxamine, oral contraceptives, caffeine
    - Inducers: Carbamazepine, phenytoin, rifampin

de Leon J. 2022; 64: 331-4.

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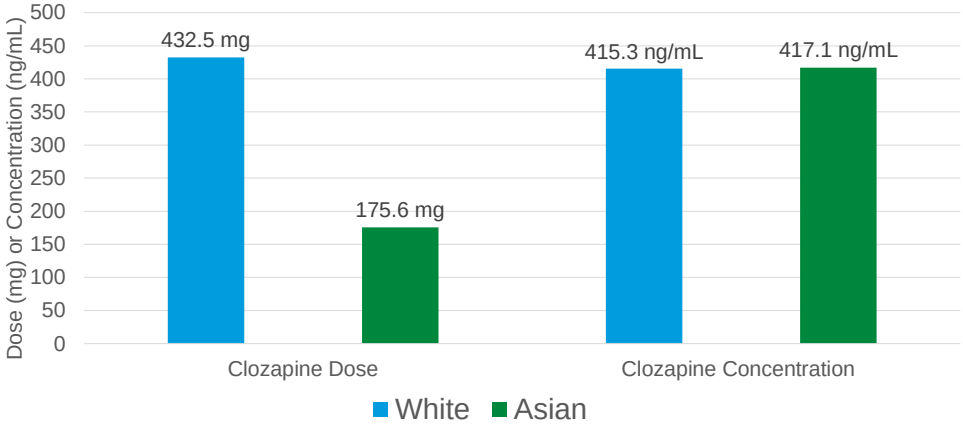
CLOZAPINE AND ANCESTRY

- White patients from Australia compared to Asian patients from Singapore (n = 40)



Ng CH, et al. 2005; 20: 163-8.

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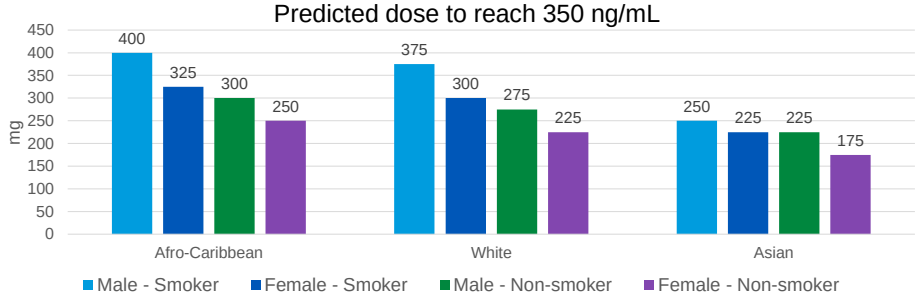
CLOZAPINE AND ANCESTRY

- UK study including 17,787 clozapine levels from 5960 patients
- Accounted for dosage form, last dose, sample timing, age, weight
- Estimated the dose to reach 350 ng/mL



Reeves, et al. Br J Clin Pharmacol. 2024 Jan;90(1):135-145.

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CLOZAPINE AND ANCESTRY

Population	Metabolism	Start Dose	Week 1 Max Dose**	Week 4+ Target**
Asian/Native American	Lower*	6.25 mg	25 mg	75 mg to 150 mg
Asian/Native American	Average	12.5 mg	50 mg	175 mg to 300 mg
European/ Western Asian^	Lower*	12.5 mg	50 mg	100 mg to 200 mg
European/ Western Asian^	Average	25 mg	100 mg	250 mg to 400 mg
American (non-Asian, non-Native American)	Lower*	12.5 mg	50 mg	150 mg to 300 mg
American (non-Asian, non-Native American)	Average	25 mg	100 mg	300 mg to 600 mg

* Due to interactions, ** female non-smokers require lower dose range, ^Asian countries west of Pakistan

de Leon, et al., 2022; 55:73-86.

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PNEUMONIA WITHOUT NEUTROPENIA

- High mortality as reviewed in the World Health Organization's VigiBase
  - 2,077 fatal cases of 6,983 total reports of pneumonia
- Several retrospective studies report increased risk of pneumonia or related hospitalizations with clozapine compared to other antipsychotics
- Risk further increased by clozapine plus another antipsychotic

Study	Outcome	Clozapine	Olanzapine	Quetiapine
Milano, 2020	PNA-related hospitalization	2.37 (95% CI, 1.30-4.32)	Not significant	Not significant
Kuo, 2012	PNA and current prescription	3.18 (95% CI: 2.62–3.86)	1.83 (95% CI: 1.48–2.28)	1.63 (95% CI: 1.15–1.91)

de Leon J, et al. 2022 55:73-86. Kuo C. 39; 2013:649-57. Milano VR. 2020; 24:20m02594.

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PNEUMONIA WITHOUT NEUTROPENIA

- Pneumonia risk in early exposure
  - Sialorrhea
  - Sedation
  - Rapid titration may contribute to acute inflammation and CYP inhibition
  - Rising clozapine levels may lead to sialorrhea, sedation, swallowing disturbances
- Pneumonia risk in chronic exposure
  - Recurrent pneumonia not uncommon
  - Hypogammaglobulinemia in more common in clozapine-treated patients
  - Series of 17 patients treated with clozapine, referred to immunology clinic:
    - Reversibility with discontinuation (n=2)
    - Need for prophylactic antibiotics (n=5)
    - IVIG treatment (n=7)

Elkhalifa S, et al. 2021; 5: 15-8. de Leon J, et al. 2022 55:73-86.

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