PSYCHIATRY CLINICAL UPDATES 2023

March 7-10, 2023
Fairmont Orchid
Kohala Coast, Big Island, Hawaii
GENETIC ANCESTRY AND DRUG METABOLISM
AN UPDATE ON CLOZAPINE SAFETY

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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

• Nothing to disclose

All relevant financial relationships have been mitigated.
LEARNING OBJECTIVES

• Review the history of clozapine
• Describe the proinflammatory influence of clozapine and risk of pneumonia
• Describe the influence of genetic ancestry and other factors on clozapine metabolism
• Develop a titration plan for clozapine accounting for a patient’s genetic ancestry
CLOZAPINE – THE PAST

1958: Development

1962: First human studies began in Europe

1970: Little use given lack of EPS

1972: Switzerland Australia

1974: West Germany, 19+ other countries

1974: US starts phase II studies

1975: Finnish deaths, European withdrawal and compassionate use

1989: US FDA Approval

THE LANCET, SEPTEMBER 27, 1975
CLOZAPINE AND AGRANULOCYTOSIS

Sir,—18 cases of severe blood disorder, 9 of them fatal (8 agranulocytosis and 1 probably leukæmia), were reported in June and July, 1975, in conjunction with clozapine treatment in Finland to the Drug Adverse Reaction Register at the National Board of Health (N.B.H.). This was an alarming accumulation of adverse reactions during such a short period in a population of about 4·6 million:

Clozapine for the treatment-resistant schizophrenic: results of a US multicenter trial

John M. Kane¹, Gilbert Honigfeld², Jack Singer², ³, Herbert Meltzer³, ⁴, and the Clozaril Collaborative Study Group*

Psychopharmacology (1989) 99: S60–S63

CLOZAPINE
USES/BENEFITS

• FDA approved for:
  • Treatment resistant schizophrenia
  • Risk reduction of recurrent suicidal behavior in schizophrenia or schizoaffective disorder

• Off-label benefits:
  • Bipolar disorder
  • Tardive dyskinesia
  • Parkinson’s related psychosis
  • Borderline personality disorder

• Lower all-cause mortality compared to other antipsychotic use

CLOzapine
Hematologic Concerns

• 1975 - Sandoz reviewed worldwide cases of agranulocytosis
  • Risk in Finland was 20 times higher compared to other countries

• 2006 - Schulte PFJ reported on risk of clozapine-induced agranulocytosis in the US
  • Months 6-12: 0.7/1,000 patient-years
  • Months >12: 0.39/1,000 patient years

• 2013 Netherlands Clozapine Collaboration Group guidelines:
  • Hematologic monitoring stopped in certain patients with low-frequency (eg, quarterly) monitoring or as clinically indicated

Griffith RW, Saameli K, 1975; 7936: 657
**VEVOX QUESTION – NEEDS FORMATTING**

**HEMATOLOGIC CONCERNS**

- MS is a 34-year-old female prescribed clozapine for schizophrenia. She is on an every 28 day frequency for ANC monitoring and has never had neutropenia.

- She arrives to the pharmacy needing a refill today. Her last ANC was entered into REMS 29 days ago. She is unable to get labs drawn until next week.

- Which of the following is true regarding clozapine in this scenario?
  
  A. The patient is unable to get clozapine today, “No blood, no drug”
  
  B. As long as the Patient Status Form is current, clozapine can be dispensed
  
  C. Only a one-time, 7-day supply can be dispensed
  
  D. None of the above
CLOZAPINE
"NO BLOOD, NO DRUG“ WITH BARRIERS AND HARM

Clozapine REMS. 2015.
CLOZAPINE
THE FDA AND COVID-19

• FDA Policy for *Certain REMS Requirements During the COVID-19 Public Health Emergency: Guidance for Industry and Health Care Professionals*
  • Several medications exist under a REMS with Elements to Assure Safe use (ETASU)
    • E.g., Laboratory testing, imaging
  • REMS remained in effect, but the FDA suggested accommodations could be made based on judgement of a health care professional
CLOzapine
International Consensus

• The frequency of ANC monitoring may be reduced to every 3 months, with dispensation of up to a 90-day supply (if it can be safely stored) for people fulfilling all of the following criteria:
  1. continuous clozapine treatment for > 1 year
  2. have never had an ANC < 2000/microL (or < 1500/microL if history of benign ethnic neutropenia)
  3. no safe or practical access to ANC testing
CLOZAPINE
UPDATED REMS AND THE PLEAS TO PAUSE

• The 2021 REMS launched on November 15, 2021

• A coordinated effort to voice concerns for foreseen patient harms
  • APA, NAMI, AAPP, etc.

• November 19, 2021: Due to inaccessibility, the FDA decided not to enforce multiple provisions of the REMS program including aspects related to purchasing, the Patient Status Form (PSF), and the REMS Dispense Authorization (RDA)
CLOZAPINE
HARMS REPORTED

• Institute For Safe Medication Practices (ISMP) reported a 40-year-old unable to access clozapine after 10 years of treatment
  • Prescriber was having difficulties registering with REMS
  • Patient went without clozapine for 2 weeks and was hospitalized
  • 80% of the dose was started resulting in cardiac arrest and anoxic brain injury

ELIMINATING CLOZAPINE REMS
UPDATES FROM THE AMERICAN ASSOCIATION OF PSYCHIATRIC PHARMACISTS

• Stakeholders and Clozapine Product Manufacturers’ Group (CPMG) continue to meet with the FDA, most recently February 4, 2023
  • Stakeholders and CPMG noted:
    • Little change in the past year
    • Ongoing treatment disruptions resulting in relapse/hospitalization
    • Worsening clozapine underutilization
    • Difficulties finding pharmacies that dispense clozapine
  • NAMI has been collecting data on patient/family REMS experiences

• An ask that REMS be eliminated or changed an educational REMS vs. the current REMS with ETASU

• The FDA noted that REMS is under internal review
CLOzapine
Escaping the Long Shadow of HEMATOLOGIC MONITORING

- A historical hyperfocus on neutropenia, blinding recognition to other concerns

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; CI = contraindication; ↑ = strengthened

* Pre-2013 Contraindications: allergy, myeloproliferative disorders, uncontrolled epilepsy, history of clozapine induced agranulocytosis, comatose states, combined with myelosuppressive agents, paralytic ileus
CLOZAPINE
ESCAPING THE LONG SHADOW OF HEMATOLOGIC MONITORING

• Where is the literature is evolving and the package insert is lacking
  • Clozapine and inflammation/CRP monitoring
  • Clozapine and pneumonia
  • Clozapine and the influence of ancestry
An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels

CLOZAPINE
A PRO-INFLAMMATORY MOLECULE

• Clozapine-related inflammation is recognized but not well understood
  • Occurs early after exposure
  • Non-specific findings are common: ↑CRP, ↑ESR, fever, and eosinophilia
  • It is unknown whether inflammatory reactions affecting different body tissues are a part of the same biologic mechanism
    • Myocarditis, hepatitis, colitis, pancreatitis, acute interstitial nephritis, etc.

• Consistent evidence from both in vitro and in vivo studies is lacking
  • Clozapine may impact macrophage/lymphocyte-mediated release of pro-inflammatory markers such as IL-6 and TNF-alpha
  • Impact may be greater in women
  • Pro-inflammatory markers may decline with chronic clozapine exposure over time

CLOZAPINE IMPACTED BY INFLAMMATION

- Acute inflammatory processes impact the cytochrome P450 (CYP) system
  - Possible cytokine-mediated mechanisms include:
    - Epigenetic modifications
    - Inhibition of CYP enzyme transcription
    - Nitric oxide-dependent proteasomal degradation of CYP enzymes
  - Effects:
    - ↓ CYP1A2, ↓ CYP2C19, ↓ CYP3A4, ↔ CYP2D6

### Table

<table>
<thead>
<tr>
<th>Factor</th>
<th>Post-hip replacement</th>
<th>During SARS-CoV-2 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2 metabolic ratio</td>
<td>↓ 53%</td>
<td>↓ 52.6%</td>
</tr>
<tr>
<td>CYP2C19 metabolic ratio</td>
<td>↓ 57%</td>
<td>↓ 74.7%</td>
</tr>
<tr>
<td>CYP3A4 metabolic ratio</td>
<td>↓ 61%</td>
<td>↓ 22.8%</td>
</tr>
<tr>
<td>CRP, IL-6, and TNF-alpha</td>
<td>Significant ↑ from baseline on days 1 and 2</td>
<td>Significant ↓ 3 months post-infection</td>
</tr>
</tbody>
</table>

Metabolic ratio = [metabolite] / [parent drug]

CLOZAPINE
INFLAMMATION AND ELEVATION OF LEVELS

Clozapine initiated

Clozapine-associated macrophage/lymphocyte activation

Acute rise of cytokines with fever, acute phase response, inflammation, etc.

Toxicity, hypersensitivity, impact on organs and other tissues

Dose escalation, cytokine-mediated CYP inhibition, pharmacogenomic factors may exacerbate process

Clozapine initiated

Clozapine-associated macrophage/lymphocyte activation

Acute rise of cytokines with fever, acute phase response, inflammation, etc.

Total clozapine levels rise, but proportion of free clozapine unchanged

↑ acute phase protein, ↑ alpha-1 acid glycoprotein which binds clozapine

- Isolated and benign?
  - Eosinophilia
  - Tachycardia
  - Myoclonic jerks
  - Sedation vs. malaise
  - Fever vs. hyperthermia
  - ↑ baseline CRP

- Systemic and severe
  - Myocarditis, hepatitis, nephritis, pancreatitis, serositis, colitis, pneumonitis, parotitis, drug reaction with eosinophilia and systemic symptoms
A 41-year-old, non-smoking, non-obese, White, woman with bipolar disorder and several past psychiatric hospitalizations presented to the emergency department with manic symptoms. Past medical history included hypothyroidism (TSH normal) and tardive dyskinesia.

Clozapine is started and titrated by 25 mg daily → 200 mg daily at bedtime.

On the third day of clozapine 200 mg – worsening sialorrhea, difficulty staying awake during the day, dizziness, and near fall.

Clozapine level: 1590 ng/mL, norclozapine level: 482 ng/mL, CRP 46.1 mg/L
VEVOX QUESTION – NEEDS FORMATTING

INFLAMMATION

• Which of the following might best explain the elevated clozapine level?
  1. Too high of a target dose for a women
  2. Undetected interaction, such as caffeine
  3. Inflammatory effects secondary to clozapine
  4. The rate of titration beyond what is typically recommended

• Dose reduced to 150 mg: clozapine level 660 ng/mL
• Dose reduced to 100 mg: clozapine level of 336 ng/mL, CRP 19.5 mg/L
CLOZAPINE
INTERNATIONAL GUIDELINE ON CLOZAPINE TITRATION AND MONITORING

• Recommendations on screening for inflammation:
  • Baseline and weekly CRP monitoring for at least four weeks to emphasis **any** inflammation detected
  • Pause clozapine titration or lowering the dose in the setting of inflammation
  • Use therapeutic drug monitoring when possible
  • “**In countries with enough resources, adding weekly troponin during the first weeks appears reasonable until studies with better outcomes are available.**”

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CLOZAPINE
PNEUMONIA WITHOUT NEUTROPENIA

• Pneumonia risk in early exposure
  • 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
  • Recurrence likely
  • Hypogammaglobulinemia in clozapine-treated patients vs. clozapine-naïve
    • Review of 17 patients treated with clozapine, referred to immunology clinic reported reversibility (n=2), prophylactic antibiotics (n=5), or IVIG (n=7)

CLOZAPINE
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

• Many retrospective cohort studies report increased risk of pneumonia or pneumonia-related hospitalizations with clozapine compared to other antipsychotics

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milano, 2020</td>
<td>PNA and hospitalization</td>
<td>2.37 (95% CI, 1.30-4.32)</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td>Kuo, 2012</td>
<td>PNA and current prescription</td>
<td>3.18 (95% CI: 2.62–3.86)</td>
<td>1.83 (95% CI: 1.48–2.28)</td>
<td>1.63 (95% CI: 1.15–1.91)</td>
</tr>
</tbody>
</table>

Guideline aims to bring awareness on early onset pneumonia with clozapine titration
  • Lack of consideration of pneumonia after chronic exposure
• No publications have assessed interventions on preventing pneumonia or recurrence
• Theoretical suggestions based on possible mechanisms
  • Treatment of sialorrhea
  • Minimizing sedation
  • Assessing aspiration risk
  • Assessing hypogammaglobulinemia after recurrence?
CLOZAPINE
PHARMACOTHERAPY AND ANCESTRY

• Concept of ethnopsychopharmacology described in the 1960s with John Cade
  • Lower dose requirements and greater side effects seen with TCAs prescribed to Asian patients as compared to White patients from Australia

• Addresses cultural and biological influences on medication response
  • E.g., CYP450 polymorphism, nutrition, environment, culture

• Landmark clozapine studies have involved limited populations
  • 1988 Kane, et al.: 65% White, 23% Black, <1% Asian
  • 2003 Meltzer et al.: 70% White, 15.4% Black, 1.2% Asian

CLOZAPINE
PHARMACOTHERAPY AND ANCESTRY

• Limitations
  • Caution with continental groupings which may oversimplify recommendations
    • E.g., HLA*B 15:02, Han Chinese vs. Japanese
  • Concepts not well studied across global settings
    • Published information has primarily focused on Asian (sub)populations
  • Advancing knowledge/technology changes interpretations
    • E.g., 1990 = CYP2D6*4 allele, 2008 = 75 variants, 2023 = 163 variants

Belle DJ, Singh H. 2008; 77:1553-60.
CLOZAPINE
PHARMACOTHERAPY AND ANCESTRY

- Despite limitations, accounting for ancestry should be considered with clozapine titration and dosing
  - Minimum concentration of 350 ng/mL is important
  - Relative to other antipsychotics, narrow therapeutic window
  - Tolerability can influence adherence
  - Global variation of CYP450 activity (e.g., 1A2, 2C19, 3A4, 2D6)

- Refining practice as more population specific data emerges
  - De Leon on the Guideline: recommendations based on “…pharmacokinetic predictions and limited data, so it is a document in progress…”
CLOZAPINE
FACTORS INFLUENCING METABOLISM

• Patient specific parameters to consider for titration and final target dose
  • Asian patients 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.
# CLOZAPINE

## ANCESTRY AND METABOLISM

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

[de Leon, et al., 2022; 55:73-86.](#)
CLOZAPINE
ASIAN ANCESTRY

• White Australian compared to Asian patients from Singapore (n = 40)

CLOZAPINE
ASIAN ANCESTRY

• CYP1A2 enzyme activity using caffeine probe
• Significant differences between Korean and Swedish populations

Ghotbi. 2007; 63: 537-46. Figure used with permission: Springer Nature.
CLOZAPINE
EXTRAPOLATIONS FROM OLANZAPINE (CATIE AND CATIE-AD DATA)

• N = 523 who provided 1,527 plasma samples for olanzapine levels

• Black or African American patients had a 26% faster clearance

• Women cleared olanzapine 38% slower

• Nearly 2-fold clearance difference between smoking, Black or African American men compared to non-smoking, non-Black or African American, women

CLOZAPINE
IN THE LAST MONTH – LANCET PSYCHIATRY

• 16,068 clozapine assays completed in the UK (n = 4,495) with genomic information available

• With genomic data 5 ancestry groups were assessed
  • European, sub-Saharan African, North African, Southwest Asian, and East Asian

• Compared to those of European ancestry:
  • Those of sub-Saharan African ancestry had ↑ clozapine metabolism
    • But had similar doses and less likely achieve levels of >350 ng/mL
  • Those of East Asian or Southwest Asian ancestry had ↓ clozapine metabolism
• 371,610 clozapine assays completed in the UK (n = 48,098) with ethnicity known in 9,412 patients, samples from 1993-2017

• Compared to White patients, the predicted dose differed for those identified as Afro-Caribbean (33% ↑) and (South) Asian (22% ↓)

• TDM data with no attempts to control for adherence, timing, other interactions
CLOZAPINE
IN THE LAST MONTH – BRITISH JOURNAL OF CLINICAL PHARMACOLOGY

• Included 17,787 samples (n = 5960)
• Excluded those with interactions, overdose, samples were during investigation of death, neonates, mixed race category
• Accounted for dosage form, date/time of last dose, date/time of sample, age, sex, weight
• Reference group: non-smoking, White male, 70 kg, 40 years of age

Predicted dose to reach 350 ng/mL
CLOZAPINE
ESCAPING THE LONG SHADOW OF HEMATOLOGIC MONITORING

• The clozapine REMS program is still a major barrier, but organizations are advocating urgent change

• Reducing hematologic monitoring after 1 year (even 18 months) is supported by data but REMS still takes precedent

• More research is needed on ways to mitigate or anticipate clozapine-associated inflammatory process and pneumonia

• Accounting for sex and ancestry during clozapine titration with therapeutic drug monitoring (where available) may help mitigate certain adverse events
QUESTIONS & DISCUSSION
THANK YOU FOR JOINING US IN THIS COURSE

Rochester, Minnesota
Phoenix, Arizona
Jacksonville, Florida