THE STORY OF CLOZAPINE

A Brief History
- First “atypical” antipsychotic
- Longest development and approval for any antipsychotic medication in US
- 1950s was the era for psychiatry drug development
  - Moving away from insulin shock therapy and prefrontal lobotomies to effective treatment options including chlorpromazine and clozapine

Receptor Binding Profile Comparison

“The Good” Effectiveness of Clozapine
- Treatment of choice in refractory schizophrenia
  - Considered gold standard
- U.S. Clozaril Trial
  - ≥ 2 other antipsychotic failures
- Preferred in patients with:
  - Treatment resistance
  - Persistent aggressiveness and hostility
  - Tardive dyskinesia
  - Persistent suicidality

Effectiveness of Clozapine
- Treatment of positive symptoms in treatment resistant patients
- Increased quality of life and longer time to discontinuation
- Clozapine lowers
  - Tardive dyskinesia
  - Risk for relapse
  - Suicide risk

Meltzer, 2012.
**Question**

The lifetime risk of suicide for patients with schizophrenia is estimated to be:

a. 5%  

b. 10%  

c. 20%  

d. 50%

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**Effectiveness of Clozapine**

- Reduction in suicidality
  - Lifetime risk in schizophrenia is 50%
  - InterSePT study demonstrated superiority of clozapine versus olanzapine in the prevention of suicide in high risk patients
  - 26% reduction in risk for suicide attempts or hospitalization to prevent suicide in clozapine versus olanzapine group

Meltzer et al, 2003

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**ANC Monitoring**

<table>
<thead>
<tr>
<th>Time after initiation of therapy</th>
<th>Monitoring frequency</th>
<th>ANC Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline up to 6 months</td>
<td>Weekly</td>
<td>≥ANC 1500/microliter or 1000/microliter if documented benign ethnic neutropenia (BEN)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>Every 2 weeks</td>
<td></td>
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<tr>
<td>Beyond 12 months</td>
<td>Monthly</td>
<td></td>
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</tbody>
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Clozaril package insert (updated 9/2015)

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**PLACE IN THERAPY**

1. No
2. Maybe
3. Yes

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**“THE BAD”**

ANC Monitoring Time after initiation of therapy, Monitoring frequency, ANC Goal.
Benign Ethnic Neutropenia

- African or Middle Eastern descent as well as other ethnic groups
- Polymorphism protects against malaria
- Prescriber verifies patient meets criteria
- ANC typically >1200/microliter
  - No increased risk for infection in these individuals

"The Bad"

- Black box warnings
  - Severe neutropenia
  - Seizure
  - Myocarditis and cardiomyopathy
  - Orthostatic hypotension, bradycardia, and syncope
  - Increased mortality in elderly patients with dementia-related psychosis
  - Clozapine REMS program

- Other warnings
  - Eosinophilia
  - QT interval prolongation
  - Metabolic changes
  - Hyperglycemia and diabetes mellitus
  - Dyslipidemia
  - Weight gain
  - Neuropenic malignant syndrome
  - Fever
  - Pulmonary Embolism
  - Anticholinergic toxicity
  - Interference with cognitive and motor performance

Berliner, 2015; CPNP, 2015.

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Clozaril package insert (updated 9/2015).

Underutilization

"…leading economists have cited underuse of clozapine for treatment resistance and suicide as one of the two greatest failures of mental health providers to practice evidence based medicine."

- Dr. Herbert Meltzer


Question

The percentage of patients estimated to be treatment-resistant and, therefore, candidates for clozapine is estimated to be:

a. 15%
b. 20%
c. 25%
d. 40%

Underutilization

- 30-40% of patients with schizophrenia considered treatment-resistant
- Numerous studies highlight low utilization, even among patients categorized as treatment-resistant
  - 11% of patients referred to CATIE trial despite meeting criteria for treatment-resistance
  - 2% of patients with schizophrenia in one Veteran’s Health Administration study
  - Less than 5% of patients with schizophrenia in the U.S.
  - Racial disparities include underuse in African Americans


"…once patients get started on clozapine, their subjective experience is sufficiently favorable that they prefer it to other treatments."

- Dr. Herbert Meltzer

Meltzer, 2012.
Transitions of Care and Clozapine

- Medication Access/REMS
  - Pharmacists play a critical role in patient and prescriber education
  - Particularly with new Clozapine REMS Program

- Smoking status

Clozapine REMS

- 10/12/2015 Clozapine REMS Program active
- Grace period ends 11/2/2015
- All patient registries are discontinued
- Inpatient and outpatient pharmacies must:
  - Designate authorized representatives
  - Train staff
  - Establish processes and procedures for dispensing
  - Maintain records

US FDA, accessed 10/7/15.

Clozapine REMS

- All prescribers, dispensers, and users of clozapine are enrolled
- Prescriber may designate a “prescriber designee”
- On 12/15/2015, all clozapine outpatients require a pre-dispense authorization prior to each dispensing
- Upon discharge, patients need to be re-enrolled by the new certified prescriber and outpatient pharmacy

CPNP, 2015.

Clozapine REMS – Key Changes

- Every patient considered “rechallengeable” if criteria for dispensing are met
- Substantial drops in ANC do not require change in frequency of monitoring unless neutropenia present
- Registering a patient requires:
  - Full name
  - Date and value of ANC
  - Gender, race, date of birth, zip code, prescriber information all as before
- Outpatient pharmacy PDA requirement


Interaction with smoking

- Clozapine is extensively metabolized CYP450 1A2
  - Polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke induce this enzyme
  - Smoking decreases clozapine levels, reducing efficacy
  - Smoking cessation leads to increased clozapine levels and toxicity
- Recommendations for dose adjustment
  - Smoking cessation: reduce dose by 40%
  - Re-initiation of smoking: resume dose prior to smoking cessation over 2 to 4 weeks

Synder et al, 2011.
OVERCOMING BARRIERS

Pharmacist’s Role

- Management of adverse effects
- Academic detailing
- Involvement in clozapine clinics

Management of Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Time</th>
<th>Action</th>
</tr>
</thead>
</table>
| Sedation             | Early, typically wears off | • Reduce dose  
|                      |                     | • Check level  
|                      |                     | • Monitor all or larger dose at bedtime |
| Hypersalivation      | Early, typically wears off, Worse at night | • Place towel on pillow at night  
|                      |                     | • Reduce dose  
|                      |                     | • Apply glycopyrrolate 2-4 mg QHS |
| Hypotension          | Early (first month) | • Reduce dose  
|                      |                     | • Slow titration  
|                      |                     | • Use caution when standing |
| Tachycardia          | Early but may persist | • Typically benign  
|                      |                     | • Consider beta-blocker  
|                      |                     | • Rule out myocarditis |


Academic Detailing

- Educational program
  - Emphasizes guidelines and evidence-based medicine
  - Targets prescribing behaviors
  - Often leads to cost savings
- VHA facility targeted clozapine underutilization
  - Surveyed providers about beliefs assessing perceived barriers
  - Patient registration, blood monitoring, patient acceptance
  - Respondents felt local support would help increase use

Farhadian et al, 2011.

Academic Detailing

- Collaborate within the system to expand prescriptive authority
- Order sets to facilitate titration and order labs
- Provide audits and feedback to prescribers
- Provide educational materials including pamphlets and toolkits for patients and providers
- Preliminary study demonstrated promising results

Farhadian et al, 2011.
**Question**

The following should be included in a clozapine order set:

a. WBC, Hgb, TSH
b. ANC, HgbA1c, lipid panel
c. Serum creatinine, weight, clozapine level
d. Norclozapine level, glucose, waist circumference

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**Pharmacist-managed Clozapine Clinic**

- Outpatient initiation of clozapine following referral from psychiatrist
- Pharmacist engaged in:
  - Patient education
  - Clinical assessment
  - Dose changes
  - Monitoring
  - Including obtaining vital signs and ordering labs
  - Prescription processing
  - Communication with PCP and psychiatrist
  - Adherence assessment

Williams et al., 2012.

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**Resources for Pharmacists**

- [College of Psychiatric and Neurologic Pharmacists](http://www.cpnp.org)
- [www.clozapinerems.com](http://www.clozapinerems.com)

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**References for clozapine content**

- Berliner N. Approach to the adult with unexplained neutropenia. In: UpToDate, Boxer LA, Drews RE (Eds), UpToDate, Waltham, MA. Accessed on October 6, 2015.
- Farhadian S, Yee MV, Christopher MLD. Fostering the use of clozapine in the severely mentally ill through academic detailing. The Mental Health Clinician 2011;1(5):94-98.