Clozapine for Schizophrenia: A Treatment Update
Ashley Khan, PharmD

Home Study Webcast
2 Slides Per Page
Clozapine for Schizophrenia: A Treatment Update

ACTIVITY DESCRIPTION
Clozapine is approved for treatment-resistant schizophrenia and suicidal behavior in schizophrenic patients. The drug has several advantages over other antipsychotics, but its safety risks concern many practitioners. In the fall of 2015, the FDA updated the prescribing information for monitoring neutropenia and approved a new shared Clozapine REMS Program. In this webinar, we will review the pros and cons of using clozapine and outline the changes implemented by the FDA.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:
- Identify the clinical manifestations of schizophrenia.
- Describe the pharmacology and clinical role of clozapine.
- Assess a regimen’s safety and efficacy based on standard monitoring parameters.
- Explain key elements of the Clozapine REMS Program.

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Universal Activity No.: 0798-0000-17-220-H01
Credits: 1.0 contact hour (0.1 CEU)

Release Date: 6/11/2018
freeCE Expiration Date: 12/11/2020
ACPE Expiration Date: 12/11/2020

ACTIVITY TYPE
Knowledge-Based Home Study Webcast

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ABOUT THE AUTHOR
Dr. Khan earned a BA in Rhetoric and Communication Studies from the University of Richmond in 2005 and a PharmD from Virginia Commonwealth University in 2009. Since then, she has practiced as a clinical pharmacist at health systems in Virginia and North Carolina, and she currently works in Investigational Drug Services at UNC Medical Center. Dr. Khan is also a medical writer and consultant at Whitsell Innovations, a company that specializes in regulatory submissions for pharmaceutical companies. She has experience with authoring documents pertaining to clinical trials, drug manufacturing, and pharmacovigilance.

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Objectives – Pharmacists

1) Identify the clinical manifestations of schizophrenia.
2) Describe the pharmacology and clinical role of clozapine.
3) Assess a regimen’s safety and efficacy based on standard monitoring parameters.
4) Explain key elements of the Clozapine REMS Program.
Objectives – Pharmacy Technicians

1) Identify the clinical manifestations of schizophrenia.
2) Describe the clinical role of clozapine.
3) Explain key elements of the Clozapine REMS Program.

Mr. M

- 46-year-old man
- Single, no children
- H/o schizophrenia
- Hears female voices calling him a beast, a pig, and a retarded animal; voices tell him to eat everything and cut his wrists
- Thinks that people are out to get him and are spying on him
- Believes that people can put thoughts into his head
Risk Factors & Pathogenesis

<table>
<thead>
<tr>
<th>Genetic Predisposition</th>
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<tbody>
<tr>
<td>Several genes likely contribute</td>
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<table>
<thead>
<tr>
<th>Perinatal Complications</th>
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<tbody>
<tr>
<td>Malnutrition</td>
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<tr>
<td>Maternal infection</td>
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<tr>
<td>Maternal stress</td>
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<tr>
<td>Preterm labor</td>
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</tbody>
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<table>
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<tr>
<th>Factors During Childhood and Adolescence</th>
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<tbody>
<tr>
<td>Infection</td>
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<tr>
<td>Brain injury</td>
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<tr>
<td>Structural brain anomalies</td>
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<tr>
<td>Neuromotor and psychosocial abnormalities</td>
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</tbody>
</table>

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<tr>
<th>Later Environmental Insults</th>
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</thead>
<tbody>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Drug abuse</td>
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</tbody>
</table>

Dopamine, glutamate, GABA, and NMDA disruptions

Schizophrenia Diagnostic Criteria

A 2 or more of the following, each present for a significant portion of time during a 1-month period

- Delusions
- Hallucinations
- Disorganized speech
- Grossly disorganized or catatonic behavior
- Negative symptoms (ie, diminished emotional expression or avolition)

B Decreased level of functioning in 1 or more major areas (eg, work, interpersonal relationships, self-care)

C Continuous signs of the disturbance persist for at least 6 months

D Schizoaffective disorder and bipolar disorder with psychotic features have been ruled out

E Disturbance is not attributable to effects of a substance or other medical condition

F If childhood-onset autism or communication disorder exists, prominent delusions or hallucinations must be present for at least 1 month

Pharmacologic Treatments

- First generation
  - Haloperidol, perphenazine
- Second generation
  - Risperidone, olanzapine
  - Clozapine

- May take 2-4 weeks to show initial response and up to 6 months to show full response
- Some early side effects may improve or resolve after the first days or weeks
Treatment-Resistant Schizophrenia

- Little or no symptomatic response to at least 2 antipsychotic trials of adequate duration (at least 6 weeks) and dose (within the therapeutic range)

- Options
  - Augmentation with
    - Other psychotropic drugs
    - Electroconvulsive therapy
  - **Clozapine**

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History of Clozapine

Clozapine is synthesized in Switzerland → Drug becomes popular in Europe and China

8 patients in Finland die of agranulocytosis; clozapine is withdrawn → FDA approves clozapine with strict monitoring requirements

Other Western countries approve clozapine → FDA approves a second indication

Indications & FDA-Approved Products

Indications
• Treatment-resistant schizophrenia
• Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder

<table>
<thead>
<tr>
<th>Brand Name Product</th>
<th>Formulation</th>
<th>Strengths</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozaril®</td>
<td>Tablet</td>
<td>12.5, 25, 50, 100, and 200 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>FazaClo®</td>
<td>Orally disintegrating tablet</td>
<td>12.5, 25, 100, 150, and 200 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Versacloz®</td>
<td>Oral suspension</td>
<td>50 mg/mL</td>
<td>No</td>
</tr>
</tbody>
</table>


Clozapine Efficacy

- Improves cognition (verbal fluency, declarative memory, attention, and speeded mental function)
- Recommended by treatment guidelines
- Patients are less likely to stop treatment because of inadequate response
- Decreases suicidality, self-harm, and all-cause mortality
- Antidepressant effects are superior to quetiapine and comparable to olanzapine and risperidone

- Reduces total and positive symptoms more than other atypical antipsychotics

Clinical Pharmacology

**Mechanism of Action**
- Proposed: antagonism of dopamine type 2 and serotonin type 2A receptors

**Absorption**
- 50%-60% absorbed
- Bioavailability unaffected by food

**Distribution**
- 97% bound to plasma proteins

**Metabolism**
- Extensive CYP450 metabolism via 1A2, 2D6, and 3A4
- Half-life ≈12 hours

**Excretion**
- ≈50% urine and 30% feces

**Clozapine Dosing**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
<td>12.5 mg once or twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Titration</strong></td>
<td>Increase by 25-50 mg/day to target of 300-450 mg/day within 2 weeks; max 900 mg/day</td>
<td>Titration decreases risk of hypotension, bradycardia, and syncope</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Continue effective dose beyond acute episode</td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>Depends on patient’s last absolute neutrophil count</td>
<td>Refer to monitoring guidelines</td>
</tr>
<tr>
<td><strong>Restart</strong></td>
<td>If &gt;2 days since last dose, restart at 12.5 mg and titrate faster</td>
<td></td>
</tr>
<tr>
<td><strong>Adjustments for Renal or Hepatic Impairment</strong></td>
<td>No specific recommendations</td>
<td>Monitor patient, may require lower dose</td>
</tr>
<tr>
<td><strong>Adjustments for Drug Interactions</strong></td>
<td>Recommended for CYP450 interactions</td>
<td>Includes cigarette smoking (moderate 1A2 inducer)</td>
</tr>
</tbody>
</table>

Therapeutic Drug Concentrations

- Clozapine plasma concentrations of 350-400 ng/mL associated with good clinical response
  - Higher concentrations don’t necessarily improve outcomes but increase likelihood of side effects

Mr. M

- Previous treatments
  - Haloperidol
  - Chlorpromazine
  - Risperidone

- Treatment at the time of hospital admission
  - Clozapine 200 mg every morning and 250 mg every night

- States he was taking his medication until 3 days ago when his group home ran out
  - Plasma concentration 127 ng/mL

- Now refuses to take clozapine but will try olanzapine
Clozapine Safety

Most common (≥5%)
- CNS reactions (eg, sedation, dizziness, headache, tremor)
- Cardiovascular reactions (eg, tachycardia, hypotension, syncope)
- Autonomic nervous system reactions (eg, hypersalivation, sweating, dry mouth, visual disturbances)
- Gastrointestinal reactions (eg, constipation, nausea)
- Fever

Black Box Warnings
- Severe neutropenia
- Orthostatic hypotension, bradycardia, syncope
- Seizures
- Myocarditis, cardiomyopathy, and mitral valve incompetence
- Increased mortality in elderly patients with dementia-related psychosis


Neutropenia

- Neutropenia: ANC < 1500/µL
- Severe neutropenia: ANC < 500/µL
  - 70% of cases are drug-related
  - Increased risk of infection

Benign Ethnic Neutropenia (BEN)

- Inherited neutropenia in certain ethnic groups
  - African descent and some groups of Middle Eastern descent
- Linked to DARC gene polymorphism
- Diagnosed by repeated ANC <1500/µL
  - ANC in patients with BEN is usually >1000/µL
- Normal neutrophil reserve in bone marrow
- No increased risk of clozapine-induced neutropenia
- No increased incidence of infection


Clozapine & Neutropenia

- Risk is greatest during the first 18 weeks of treatment
- Possible mechanisms: immune-mediated; increased neutrophil destruction; direct toxicity against precursors
- NOT dose-related
- Some patients develop transient neutropenia
- Usually fully reversible when clozapine is stopped

Clozapine Rechallenge After Severe Neutropenia

Not recommended, BUT risk of serious psychiatric illness may outweigh risk of rechallenge

Rechallenge-associated neutropenia tends to occur faster and is more severe than during the initial treatment with clozapine

Monitoring: General Population

<table>
<thead>
<tr>
<th>ANC</th>
<th>Treatment Recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range: ANC ≥ 1500/µL</td>
<td>Initiate treatment If interrupted: &lt; 30 days, continue monitoring as before ≥ 30 days, monitor as if new</td>
<td>Weekly for first 6 months Every 2 weeks from 6-12 months Monthly after 12 months</td>
</tr>
<tr>
<td>Mild neutropenia: ANC = 1000-1499/µL</td>
<td>Continue treatment</td>
<td>3 times/week until ANC ≥ 1500/µL → return to last “normal range” interval</td>
</tr>
<tr>
<td>Moderate neutropenia: ANC = 500-999/µL</td>
<td>Recommend hematology consult Interrupt treatment until ANC ≥ 1000/µL</td>
<td>Daily until ANC ≥ 1000/µL → 3 times/week until ANC ≥ 1500/µL → weekly x 4 weeks → return to last “normal range” interval</td>
</tr>
<tr>
<td>Severe neutropenia: ANC &lt; 500/µL</td>
<td>Recommend hematology consult Interrupt treatment Do not rechallenge unless prescriber determines benefit outweighs risk</td>
<td>Daily until ANC ≥ 1000/µL → 3 times/week until ANC ≥ 1500/µL If rechallenged, resume treatment as a new patient under “normal range” monitoring</td>
</tr>
</tbody>
</table>
# Monitoring: BEN Population

<table>
<thead>
<tr>
<th>ANC</th>
<th>Treatment Recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Normal range: ANC ≥ 1000/µL (obtain ≥2 baseline levels) | Initiate treatment | Weekly for first 6 months  
If interrupted:  
<30 days, continue monitoring as before  
≥30 days, monitor as if new | Every 2 weeks from 6-12 months  
Monthly after 12 months |
| Moderate neutropenia: ANC = 500-999/µL | Recommend hematology consult Continue treatment | 3 times/week until ANC ≥1000/µL or ≥ known baseline  
weekly x 4 weeks  
return to last “normal range” interval |
| Severe neutropenia: ANC < 500/µL | Recommend hematology consult | Daily until ANC ≥ 500/µL  
Interrupt treatment  
Do not rechallenge unless prescriber determines benefit outweighs risk | 3 times/week until ANC ≥ baseline  
If rechallenged, resume treatment as a new patient under “normal range” monitoring when ANC ≥1000/µL or at known baseline |

Mr. M

- No improvement with olanzapine and divalproex sodium  
  - Patient asked to restart clozapine  
- Enrolled in Clozapine REMS Program  
  - Baseline ANC 4900/µL  
  - Clozapine 12.5 mg BID initiated
Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program

- FDA launched a new Clozapine REMS Program in October 2015
  - Single, shared registry for monitoring and management
  - Requires prescribers, pharmacies, distributors, and patients to enroll
  - Rolled out in phases
- Key changes
  - Only report ANC; WBC no longer required
  - Guidelines for patients with BEN

Clozapine REMS Program: Prescriber Responsibilities

- Only prescribers and their designees can enroll patients
  - Online, by phone, or by fax
- Prescribers maintain a list of patients and:
  - Report ANCs
  - Update treatment status
  - Update monitoring frequency
  - Submit treatment rationales


Clozapine REMS Program: Prescriber Responsibilities, cont.

- Automated system notifies prescriber if a patient meets criteria for neutropenia
  - Prescriber must follow up with appropriate action


Clozapine REMS Program: Pharmacy Responsibilities

- Pharmacies must certify in the program to purchase and dispense clozapine
- Each pharmacy designates an authorized representative
- Each pharmacist enrolls and chooses at least 1 associated pharmacy

Clozapine REMS Program: Outpatient Pharmacies

• Must obtain a “predispose authorization” (PDA) before dispensing clozapine
  • Electronic code indicates that the registry has verified the patient’s eligibility
  • Dispense enough clozapine to treat the patient until the next blood draw, or as directed by the prescriber


Clozapine REMS Program: Inpatient Pharmacies

• Verify patient eligibility before dispensing clozapine for the FIRST time
• Verify that the ANC is current and acceptable according to the patient’s ANC monitoring schedule or that the prescriber has provided a treatment rationale
  • Verify in registry OR the inpatient medical record
  • ANC must be submitted within 7 days of the blood draw date

Mr. M

- Within ~2 weeks, Mr. M already had
  - Fewer negative thoughts
  - Fewer auditory hallucinations
  - No visual hallucinations
  - No suicidal ideation
- Discharged from hospital on clozapine
  - 75 mg every morning and 100 mg every night at bedtime
  - Last ANC = 4600/µL
  - No notable adverse effects

Current Trends

- Gold standard for treatment-resistant schizophrenia and reducing suicidality but...
  - Underused in primary population
  - Variable prescribing across countries
  - Safety risk is the most common reason for low comfort levels among prescribers
Exam Questions:

1. Positive symptoms of schizophrenia include:
   a. Delusions
   b. Tardive dyskinesia
   c. Flat affect
   d. Hearing loss

2. Clozapine is FDA-approved for which of the following indications?
   a. Treatment-resistant schizophrenia
   b. Reducing suicidal behavior in patients with schizophrenia and schizoaffective disorder
   c. A and B
   d. None of the above

3. According to the prescribing information, interactions between clozapine and what type of drugs may warrant dose adjustments?
   a. Calcium-containing drugs
   b. Cytochrome P450 (CYP450) inducers/inhibitors
   c. Insulin products
   d. Anticoagulants

4. Which of the following dosage forms of clozapine is currently available in the United States?
   a. Immediate release tablet
   b. Orally disintegrating tablet
   c. Oral suspension
   d. All of the above

5. A common adverse event (occurring in ≥5% of patients) with clozapine treatment is:
   a. QT prolongation
   b. Seizures
   c. Drowsiness
   d. Hallucinations

6. According to the Clozapine REMS Program, which laboratory value must be routinely monitored for all patients on clozapine?
   a. White blood cell count
   b. Red blood cell count
   c. Absolute neutrophil count
   d. A and C
7. Which of the following is true about benign ethnic neutropenia (BEN)?
   a. Individuals have a normal neutrophil reserve in bone marrow.
   b. BEN is transmitted by bodily fluids.
   c. The absolute neutrophil count in individuals with BEN is usually less than 500/µL.
   d. BEN significantly increases the risk of developing clozapine-induced neutropenia.

8. Before dispensing clozapine to a patient, which of the following should be verified?
   a. The patient is enrolled in the Clozapine REMS Program
   b. The prescriber is certified in the Clozapine REMS Program
   c. The patient's ANC is current and acceptable
   d. All of the above

9. Why would a prescriber submit a treatment rationale to the Clozapine REMS Program?
   a. To authorize rechallenge with clozapine after severe neutropenia
   b. To authorize a large dose increase
   c. To authorize a change in monitoring frequency
   d. To authorize treatment discontinuation

10. The Clozapine REMS provides a predispense authorization (PDA) for clozapine in which of the following settings?
    a. Inpatient pharmacies
    b. Outpatient pharmacies
    c. A and B
    d. None of the above