First Steps: Considering Clozapine for your Patients

The Care Transitions Network
Objectives

• At the completion of this webinar, listeners will be able to

  1. Identify the characteristics of patients who would benefit from clozapine treatment

  2. Describe the steps needed to be completed before a patient starts clozapine
Outline

• Indications for clozapine
• Before Starting clozapine
• Clozapine REMS Program
Indications for Clozapine
FDA-approved indications for Clozapine

• Clozapine is an antipsychotic that is clinically reserved for patients with Schizophrenia who are treatment resistant to standard antipsychotic therapy.

• Clozapine should be considered for any patient with schizophrenia who has persistent positive symptoms despite two trials with different antipsychotics of adequate duration and dose with adherence of ≥80% of prescribed dose taken.

• In December 2002, the US Food and Drug administration approved clozapine for treatment of recurrent behavior in patients with schizophrenia or schizoaffective disorder who are at chronic risk for suicide.
What is adequate duration?

• For acute treatment of multi-episode schizophrenia, treatment trials should be at least 6 weeks to observe optimal response.

• For acute treatment of first episode schizophrenia, a 16 week trial is considered adequate.

Howes et al. 2016
Gallego et al 2011
What is adequate dose?

- In people with treatment-responsive multiple episode schizophrenia experiencing and acute exacerbation:

- FGA: Dose equivalent to Chlorpromazine 600mg daily

Howes et al 2016
What is an adequate dose?

<table>
<thead>
<tr>
<th>First Generation Antipsychotics</th>
<th>Equivalent to 100mg Chlorpromazine</th>
<th>Minimum Therapeutic Requirement (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHENOTHIAZINES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>≥ 12</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5</td>
<td>≥ 30</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10</td>
<td>≥ 60</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>≥ 600</td>
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<tr>
<td>Thioridazine</td>
<td>100</td>
<td>≥ 600</td>
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<tr>
<td>BUTYROPHENONE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>≥ 12</td>
</tr>
<tr>
<td>OTHER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiothixene</td>
<td>5</td>
<td>≥ 30</td>
</tr>
<tr>
<td>Molindone</td>
<td>10</td>
<td>≥ 60</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10</td>
<td>≥ 60</td>
</tr>
</tbody>
</table>

Howes et al 2016
What is an adequate dose?

**Second Generation Antipsychotics**

Aripiprazole 10-30mg*
Olanzapine 10-20mg*
Paliperidone 3-15mg
Quetiapine 300-750mg*
Risperidone 2-6mg
Ziprazidone 80-160mg*

*There is insufficient evidence to determine upper effective dose limit. Upper dose is FDA-approved upper dose.

PORT Guidelines 2009
Off-label indications for Clozapine

- Clozapine is sometimes used for patients who are treatment intolerant or especially sensitive to antipsychotic agents.

- This includes patients who are sensitive to the extrapyramidal side effects from antipsychotics, who have had several dystonic reactions, or who have developed any tardive variant such as tardive dyskinesia, tardive dystonia, or tardive akathisia.

Bleakley and Taylor 2013
Off-label indications for Clozapine

• Clozapine is sometimes used for the treatment of refractory mania.

Bleakley and Taylor 2013

• PORT guidelines recommend a trial of clozapine should be offered for people with schizophrenia who present with persistent symptoms of hostility and/or display persistent violent behaviors.

PORT Guidelines 2009
Before Starting Clozapine
Determine Appropriateness for Therapy

• Start with the history.
• Based on the patient's timeline of symptoms, determine whether the patient meets criteria for clozapine treatment based on diagnosis.
• Carefully evaluate for previous trials with attention to potentially modifiable causes of non-response such as inconsistent adherence, trials at suboptimal doses, or trials of suboptimal length.
• Carefully document relevant history.
Consider adequate trials or LAI

• If history reveals inadequate trials of antipsychotic treatment, consider increasing oral therapy to optimal dose and optimal duration of treatment.

• Long Acting Injectable (LAI) medication eliminates covert non-adherence as a cause of poor response. If a patient has inadequate response to a LAI trial you can be much more confident that clozapine is indicated.
Talking to Patients and Family

• Be mindful of any negative feelings you may have about clozapine, how you present the option can influence patient and family attitudes.

• Discuss the recommendation for clozapine and its advantages first.

• Explore initial rejections, concerns, or questions as opportunities for psychoeducation.
Talking to Patients and Family

• It is important that patients and families understand that we cannot predict the extent of response to clozapine.

• That being said, **OVER 50%** of patients will have a meaningful clinical improvement on clozapine.

• Some patients have a **VERY** dramatic improvement on clozapine.
Talking to Patients and Family

• We don’t know the extent of improvement until we try it and only then can we really assess the benefit-to-risk ratio.

• We will generally know within three months how well it is going to work, but improvement can continue well beyond that.

• Clozapine is being recommended because it would be a shame to miss the opportunity to experience a real benefit.

• Once the patient is interested, then talk about the potential disadvantages as part of an informed consent process.
Review Potential Side Effects

• Clozapine carries 5 Black Box Warnings:
  • Neutropenia
  • Orthostatic Hypotension, Bradycardia, Syncope
  • Seizures
  • Myocarditis/Cardiomyopathy
  • Dementia-Related Psychosis

• Clozapine also has additional side effects.
  • CNS
  • Cardiovascular
  • Autonomic
  • Gastrointestinal
  • Fever
Review Potential Side Effects

• The first one to review is agranulocytosis, as this will require the patient to obtain frequent bloodwork.

• Patients should also be aware of the need for consistent adherence.

• Clozapine side effect management and monitoring will be reviewed in detail in an upcoming webinar.
Risk Evaluation Mitigation Strategy

- A national registry to monitor bloodwork prior to dispensing medication and to keep track of previous history of clozapine-induced neutropenia and agranulocytosis.
- Physicians and others who prescribe must pass an exam as part of the registration process.
- Who must be registered
  - The Patient
  - The Physician or other prescriber
  - The Pharmacy dispensing the medication
- www.clozapinerems.com
Coordinating Care

- Coordinating key players in order to order, receive, and review labs in a timely manner (psychiatrist, nurse, support staff, laboratory vendor, dispensing pharmacy, patient).

- Provide pharmacy with requisite laboratory data to allow for dispensing clozapine.

- Pharmacies can’t dispense clozapine without documentation of acceptable ANC levels drawn within 7 days.
Coordinating Care

• Issuing clozapine prescriptions on an ongoing basis (having a backup for continued prescribing and monitoring when psychiatrist is unavailable or on vacation).

• Monitoring the patient’s medical and psychiatric condition while taking clozapine.

• Coordinating care with primary care provider including letter sent explaining decision to begin clozapine.
Baseline Labs and Clinical Information

• Psychiatric evaluation documenting rationale for clozapine trial.

• History and Physical exam (attention to cardiac risk, constipation and baseline bowel function, thrombophilias and DVT/PE risk/history)

• Psychoeducation about clozapine provided to patient and family.
Baseline Labs and Clinical Information

- CBC with differential for ANC forwarded to pharmacy within 7 days of first dispensing first prescription.

- Vital signs including temperature, BMI, fasting glucose and lipids documented within 30 days of initiating treatment.

- EKG for QTc and arrhythmia risk
Clozapine REMS Knowledge Assessment

Clozapine and the Risk of Neutropenia
Risk Evaluation Mitigation Strategy

• Physicians and others who prescribe must pass an exam as part of the registration process.

• The exam tests knowledge on the risk of severe neutropenia with clozapine.

• We will review the risk of clozapine-induced agranulocytosis, including information relevant to passing this exam.
What is the risk of severe neutropenia?

• White Blood Cells are immune cells in blood that protect the body from infection.
• Neutrophils (or granulocytes) are one type of white blood cell.
• Clozapine is associated with severe neutropenia, or insufficient amount of neutrophils for a small percentage of patients.
• Severe neutropenia (or agranulocytosis) is defined as an Absolute Neutrophil Count (ANC) < 500/µL.
• The risk of severe neutropenia is serious infection and death.
The Clozapine REMS Program

• The goal is to minimize the risk of severe neutropenia

• The Clozapine REMS Program provides a central point of access for
  • Prescribers to certify before prescribing clozapine
  • Pharmacies to certify before dispensing clozapine
  • Patients to be enrolled and ANC values to be recorded and checked
Severe Neutropenia

• Rare in the first 4 weeks for clozapine naïve patients

• Risk rises at week 4 and peaks between weeks 12-16, then falls.

• 80-95% of cases occur within the first 6 months.

• Unlike clozapine naïve patients, rechallenged patients may be at increased risk from the start of treatment.
Severe Neutropenia

• The mechanism is thought to be immune mediated response vs. direct bone marrow toxicity.

• Severe neutropenia, when it occurs, is dose independent.

• Incidence: 1% of patients on clozapine prior to implementation of national registry monitoring system, thereafter 0.38%.

• More common in women and in those at extremes of age.
<table>
<thead>
<tr>
<th>ANC Level (General Population)</th>
<th>Treatment Recommendations</th>
<th>Frequency of ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range: ANC ≥ 1500/mm³</td>
<td>Initiate Rx</td>
<td>Weekly in first 6 months</td>
</tr>
<tr>
<td></td>
<td>If Rx interrupted</td>
<td>Every 2 weeks from 6-12</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 days, continue monitoring</td>
<td>months</td>
</tr>
<tr>
<td></td>
<td>≥ 30 days, monitor as if new pt</td>
<td>Monthly after 12 months</td>
</tr>
<tr>
<td>Mild neutropenia: ANC ≥ 1000-1499/mm³</td>
<td>Continue Rx</td>
<td>Thrice weekly until ANC ≥ 1500/mm³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Then return to pt’s last “normal range” schedule</td>
</tr>
<tr>
<td>Moderate neutropenia: ANC ≥ 500-999/mm³</td>
<td>Hematology consultation</td>
<td>Daily until ANC ≥ 1000/mm³</td>
</tr>
<tr>
<td></td>
<td>Stop treatment</td>
<td>Thrice weekly until ANC ≥ 1500/mm³</td>
</tr>
<tr>
<td></td>
<td>Resume once ANC ≥ 1000/mm³</td>
<td>Weekly for 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Then return to pt’s last “normal range” schedule</td>
</tr>
<tr>
<td>Agranulocytosis: &lt;500/mm³</td>
<td>Hematology consultation</td>
<td>Daily until ANC ≥ 1000/mm³</td>
</tr>
<tr>
<td></td>
<td>Stop treatment</td>
<td>Thrice weekly until ANC ≥ 1500/mm³</td>
</tr>
<tr>
<td></td>
<td>Only rechallenge if benefits &gt; risks</td>
<td>If rechallenged, resume monitoring as if new patient</td>
</tr>
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</table>
Benign Ethnic Neutropenia

- Benign ethnic neutropenia (BEN) occurs in 25-50% of people of African descent and has been reported in Jewish, Middle Eastern, and Afro-Caribbean groups.
- It is thought to occur because mature granulocytes are retained in the marrow storage pool rather than being released to peripheral circulation.
- It is the most common cause of neutropenia but is not associated with agranulocytosis or impaired immune system.
<table>
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<tr>
<th>ANC Level (BEN Population)</th>
<th>Treatment Recommendations</th>
<th>Frequency of ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild neutropenia: ANC ≥ 1000-1499/mm³</td>
<td>Mild Neutropenia is normal range. Obtain at least 2 baseline ANC levels before initiating Rx. If Rx interrupted &lt; 30 days, continue monitoring ≥ 30 days, monitor as if new pt.</td>
<td>Weekly in first 6 months. Every 2 weeks from 6-12 months. Monthly after 12 months.</td>
</tr>
<tr>
<td>Moderate neutropenia: ANC ≥ 500-999/mm³</td>
<td>Hematology consultation. Continue Rx.</td>
<td>Thrice weekly until ANC ≥ 1000/mm³ or ≥ pt’s baseline. Weekly for 4 weeks. Then return to pt’s last “normal BEN range” schedule.</td>
</tr>
<tr>
<td>Agranulocytosis: &lt;500/mm³</td>
<td>Hematology consultation. Stop treatment. Only rechallenge if benefits &gt; risks.</td>
<td>Daily until ANC ≥ 500/mm³. Thrice weekly until ANC ≥ 1000/mm³ or ≥ pt’s baseline. If rechallenged, resume monitoring as if new patient.</td>
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</table>
Prescriber Requirements

• Prescribers must certify in the Clozapine REMs program to prescribe clozapine.
• Must enroll all patients receiving clozapine in the Clozapine REMS program.
• Must report patient ANC to the Clozapine REMS program for each prescription of clozapine.
Patient Requirements

• Must be enrolled in the Clozapine REMS program by their prescriber
• Must comply with ANC testing requirements
Pharmacy Requirements

• Must certify in the Clozapine REMS Program to dispense clozapine.
• Must verify the prescriber is certified and the patient is enrolled.
• Prior to dispensing clozapine
  • Must verify the ANC is current and acceptable for each patient
  • Or, the prescriber authorized continuation of clozapine by providing treatment rationale
Parting Thoughts

• **OVER 50%** of patients will have a meaningful clinical improvement on clozapine. Some patients have a VERY dramatic improvement.

• For patients with treatment-resistant Schizophrenia, it would be a shame to miss the opportunity to experience a real benefit.

• We won’t know the extent of improvement for a given patient unless and until clozapine is tried.
References


• Uptodate.com


Thank you!

www.CareTransitionsNetwork.org
CareTransitions@TheNationalCouncil.org

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