Clozapine

NCDPS Health Services
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Disclosure
NC Department of Public Safety
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Health Services- Nursing Education NCNA Approved Provider
Title: Clozapine
To receive contact hours nurses must complete 100% of this CNE activity and complete the evaluation in Survey Monkey

Neither the speaker nor members of the planning committee have any conflicts of interest related to the content of this activity.

NC Department of Public Safety, Division of Adult Corrections/Prisons Health Services is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation
Title: Clozapine

Learning Outcome:
Licensed Health Services staff attending this session will be able to identify:

- What is Clozapine?
- What Clozapine is used to treat?
- The major side effects of Clozapine?
- Why regular blood testing is required?
- What is the nursing role in Clozapine Treatment?
References

- “Clozapine for Self-Injurious Behavior: Beyond Schizophrenia”, Brian Sheitman, MD and Ted Zarzar, MD; Department of Psychiatry UNC School of Medicine and NC DPS, April 2017.
- Shriver.umassmed.edu/.../Clozapine%20Therapy%20Training%20FINAL%203-10-15...Clozapine Therapy Training. 3/10/2015.
- https://www.samhsa.gov/
- NCDPS Health Services Policy & Procedure Manual; Section: Care and Treatment of Patient; Use of Clozapine
Clozapine

- “Atypical” *Antipsychotic medication. Brand name is Clozaril.
- Used primarily in the treatment of **Schizophrenia** and **Schizoaffective Disorder** when other medications have been tried and failed or have caused serious side effects.
- The goal of Clozapine therapy is to **eliminate the symptoms of Schizophrenia/Schizoaffective Disorder** such as hallucinations and delusions.

*A“Atypicals” have less extra-pyramidal side effects* (tremors, rigidity, dystonias)

Antipsychotics also known as **neuroleptics** or major **tranquilizers**, are a class of medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder.
Schizophrenia

- Schizophrenia is a severe, chronic, brain disorder that distorts the way a person thinks, acts, expresses emotions, perceives reality and relates to others.

- Symptoms may include: hallucinations (hearing voices or seeing people or things that are not real), delusions (believing things that are not true), trouble organizing thoughts, flat affect, showing a lack of pleasure for life or activities, having trouble focusing or paying attention.
Schizoaffective disorder

- Schizoaffective disorder is when the individual has symptoms of schizophrenia (such as hallucinations or delusions) and also experiences symptoms of a mood disorder (such as major depression, mania or bipolar disorder).

- Schizophrenia and/or Schizoaffective Disorder may impact all areas of daily living for an individual including home, work, social contacts and relationships. Some individuals diagnosed with Schizophrenia or Schizoaffective Disorder may show signs of suicidal behavior.

While there is no cure for Schizophrenia or Schizoaffective Disorder, symptoms can often be controlled with proper treatment including the use of antipsychotic medications.
Clozapine - History

- Discovered in 1958 by a Swiss pharmaceutical company, based on the chemical structure of the tricyclic antidepressant imipramine. **The first test in humans in 1962 was considered a failure.**
- Trials in Germany in 1965 and 1966 and a trial in Vienna in 1966 were successful.
- **In 1972-1975 clozapine was released in Europe as Leponex.**
- The “Finnish epidemic” – September, 1975
  - **A report of 18 patients** on clozapine developed **blood disorders & 9 died.**
- Clozapine was voluntarily **withdrawn by the manufacturer.** FDA trials in the U.S. are halted.
- However, **when studies demonstrated that clozapine was more effective against treatment-resistant schizophrenia** than other antipsychotics, the FDA and health authorities in most other countries approved its use only for treatment-resistant schizophrenia, and required Restricted Distribution, a Patient Registry and regular **hematological monitoring.**
Clozapine - History

- In Study #30\(^1\) in 1984 in the US
  - The FDA mandated that superiority to other drugs be shown, not just superiority to a placebo.
- **Results were overwhelmingly in favor of clozapine.**
- Clozapine approved by the FDA in 1989 for:
  - Treatment-resistant schizophrenia
  - Reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders (came at a later date)
- **Monitoring mandate:** weekly CBCs for 6 months followed by bi-weekly or every 2 weeks CBCs for 6 months followed by monthly CBCs thereafter for treatment course.

\(^1\)Kane et al., *Arch Gen Psychiatry*, 1988
Broad Range of Effectiveness

Clozapine may have utility for a variety of other disorders and conditions:

- treatment of hostility and aggression
- treatment-resistant bipolar disorder
- psychogenic polydipsia/hyponatremia
- Parkinson Disease Psychosis and psychosis in Lewy-Body dementia
- Borderline Personality Disorder
- tardive dyskinesia (TD)

Growing evidence also suggests clozapine may be an option in youth with early onset schizophrenia

Clozapine is the only antipsychotic with a Food and Drug Administration approval for suicidality and it has the lowest mortality rate among all antipsychotic treatments

https://www.samhsa.gov/
Conventional Management of Aggression/SIB

**Acute Management** includes:
- Intramuscular (sedating) medications
  - Haloperidol, lorazepam, olanzapine, ziprasidone, chlorpromazine
- Nicotine replacement
- Seclusion/isolation/restraint
- Ignore the behavior
- Discharge

**Long-term Management** includes:
- Antidepressants, mood stabilizers, antipsychotics, benzodiazepines, beta-blockers
- Cognitive behavioral / Dialectical behavioral therapy
  - Focus is distress tolerance, emotion regulation, mindfulness, establishing safe coping mechanisms
- Individual and group modalities
- Behavioral plans
- Ignore behavior
- Transfer somewhere else

- Evaluation of antipsychotic use and mortality
- **66,881 patients with schizophrenia** treatment between 1996-2006
- **Clozapine associated with lowest risk of death** from any cause, from suicide, and from ischemic heart disease.
- Long-term (7-11 yrs.) of exposure to antipsychotic treatment associated with lower mortality than no treatment at all.
Common Clozapine Side Effects

- Constipation
- Drooling
- Sedation
- Increased Sweating
- Weight Gain/metabolic
Serious Side Effects

- Agranulocytosis
- Seizures
- Orthostatic Hypotension
- Bradycardia
- Syncope
- Myocarditis
- Cardiomyopathy
- Colitis
Agranulocytosis Potentially Fatal Blood Disorder

The healthy body has an immune system which resists and fights infection. White blood cells are the infection fighting cells in the blood.

- Agranulocytosis is when too few or no white blood cells (or WBCs) are made, reducing the body’s ability to resist and fight infection.

When an individual receives Clozapine, there is risk of Agranulocytosis. Without white blood cells the body does not have a natural defense against even common bacteria and viruses such as the common cold. Therefore, if an individual had a low white blood cell count and they caught a common cold it could be fatal!

Peak risk in Clozapine treatment:
- Between 2 & 4 months of treatment
- 95% of the cases occur by 24 weeks

If Agranulocytosis is caught in the early stages it can be treated and reversed.
Myocarditis Risk

- **Myocarditis** - is inflammation of the heart muscle. A severe case can weaken the heart, which can lead to heart failure, abnormal heartbeat, and sudden death.

- **Signs of infection or myocarditis:**
  - fatigue, dyspnea, chest pain, peripheral edema, persistent palpitations, fever, flu-like symptoms

- Myocarditis typically occurs within the first 4 weeks
Is It Worth the Risk?

- Patients at **Central Prison** were offered **clozapine** for the same indications as would be used at the NC state psychiatric hospitals or at UNC [NOT experimental or research but the community standard].

- For **Severe self injury and assaultive behaviors** secondary to **personality disorders**, as well as **treatment resistant schizophrenia patients**.
Clozapine in Correctional Healthcare

- Every correctional health care system should have a system that provides ready access to clozapine or establishes mechanisms for referral of patients who are appropriate for treatment with clozapine.

- Every correctional health care system should have policies and procedures to facilitate the safe and appropriate use of clozapine.

- Every correctional health care system should provide appropriate safety monitoring of patients receiving clozapine.
Why? Clozapine in Corrections

- Clozapine has been effective for a variety of conditions:
  - treatment of hostility and aggression
  - treatment-resistant bipolar disorder
  - psychogenic polydipsia/hyponatremia
  - Parkinson Disease Psychosis and psychosis in Lewy-Body dementia
  - Borderline Personality Disorder
  - tardive dyskinesia (TD)

- Growing evidence also suggests clozapine may be an option in youth with early onset schizophrenia
Clozapine is the only antipsychotic with FDA [Food and Drug Administration] approval for suicidality and it has the lowest mortality rate among all antipsychotic treatments.
Cost Effectiveness

- Study with 479 clozapine patients compared to 2240 other medicated patients.
- Reviewed 6 months prior to treatment and 12 months post initiating of treatment.
- Findings: Significantly fewer emergency department visits
- Significantly lower overall cost
  - $21,315 lower in all general cost [no matter what the cause]
  - $17,457 lower mental illness related cost
  - $10,582 lower cost for schizophrenia treatment

Will Treatment Be Cost Effective in Corrections? How to get started...

Criteria for Clozapine treatment at Central Prison:

- Repeated episodes of self-injury, suicide attempts.
- Willingness to have blood drawn weekly.
- Able to give informed consent.
- Willingness to take medication regularly.
Coordinated policies for clozapine treatment using the NC state hospitals guidelines.

DPS HS at CPHF [Central Prison Healthcare Facility]
Completed Policy June 2016

A team approach with an experienced second psychiatrist to review patient indication.

*See most recent policy on DPS website or facility SOP
2nd Step to Coordinate Team

DPS HS at CPHF

Other team members:

- Pharmacy
- Medical service
- Nursing
- Lab
- Psychiatry
- Psychology
Providers’ Role

Medical, Psychiatry, Psychology, Pharmacy:

- Establish patient meets criteria
  - Patient has DSM 5 diagnosis [schizophrenia, schizoaffective disorder, refractory bipolar, borderline personality disorder]
- Registered on FDA Clozapine REMS Program
- Approved pharmacy designee to enter ANC results
- Education/Informed Consent [risks; no labs no medication]
- Order monitoring labs before treatment, during treatment, and at discontinuation of treatment
- EKG baseline and as needed
- Write notes re: reasonable approach, and checks for labs re: ANC and myocarditis monitoring.
Pharmacy’s Role

- **Registered** on FDA Clozapine REMS Program and will enter ANC values in database before filling order.
- Pharmacist **will not dispense** clozapine **unless have** patients blood test results.
- Pharmacist will report **need to stop** clozapine to provider.
- Pharmacist will monitor other medications patient is on since **many medications interact with clozapine**.
Nursing’s Role

- Monitor Labs & EKG completed and acceptable before medication initiated.
- Evaluate & reinforce patient’s understanding of treatment including side effects, consent signed, and adherence to blood collection schedule.
- Monitor patient compliance in taking medication.
- Monitor for potential side effects and symptoms of infection or myocarditis.
- Monitor Vital Signs.
Nursing’s Role

Notify provider:

- Interruption in treatment greater than 48 hrs.
- ANC less than 1500 for GP [General Population] patients or less than 1000 for BEN [Benign Ethnic Neutropenia]* pts. [need for further testing]
- If CBC not drawn on designated day, Nurse Supervisor on unit request CBC within 24 hrs.
- **Signs of infection or myocarditis:** fatigue, dyspnea, chest pain, peripheral edema, persistent palpitations, fever, flu-like symptoms
- If scheduled Labs are late 2 days, pass scheduled time Clozapine will be discontinued unless CBC immediately obtained.

*BEN – Benign Ethnic Neutropenia: ethnic group with an average ANC lower than standard values. Normal for individuals from African, Middle East, other non-Caucasian descent
Lab’s Role

- Timely collection of ordered labs.
- Report of abnormal labs ASAP.
- Notify nursing if lab unable to collect specimen.
Patient’s Role

- Demonstrates understanding of consent.
- Informed consumer.
- Reports side effects, and or signs and symptoms of infection or myocarditis.
- Takes medication daily at same time.
- Adheres to lab collection schedule
  \[\text{no labs} \rightarrow \text{no medication}\].
3rd Step to Identify Eligible Patients

DPS HS at CPHF

- Patients on unit 2100 at CP were identified that met the criteria for clozapine trial.

Criteria for Clozapine treatment at Central Prison

- Repeated episodes of self-injury, suicide attempts.
- Willingness to have blood drawn weekly.
- Able to give informed consent.
- Willingness to take medication regularly
Careful Monitoring per FDA REMS-
(Risk Evaluation and Mitigation Strategy) done at CPHF

Baseline labs/tests and every week for 4 weeks:
- CBC w/ diff
- Myocarditis panel: C-reactive protein, pro-BNP, troponin, CK/MB
- EKG

Then CBC every week for 6 months, if acceptable, then every 2 weeks for 6 months, if acceptable then monthly while on treatment.

- Clozapine initiated by slow titration.

- Daily Vitals initiated, but had poor adherence. [Check for pulse elevation which could be a sign of myocarditis; or fever could be a sign of low WBC’s].
Staff Monitoring for **Side Effects**

- **Most Common Reported:**
  - Sedation
  - Orthostasis/dizziness
  - Drooling
  - Tachycardia
  - Anticholinergic (dry mouth, constipation)
  - Appetite increase, metabolic syndrome

- **Less common:**
  - ~1% risk of agranulocytosis
  - ~1-3% risk of myocarditis
  - Lower seizure threshold
Will all the monitoring work in Corrections?

- Would patients agree to try clozapine?:
  13 patients met criteria and offered clozapine. **10 agreed** and started clozapine treatment. Only 2 patients have stopped the medication.
  4 patients on treatment for greater than 6 months.
- Would patients allow their blood to be drawn regularly? **YES**
- Would patients take the medication regularly? **YES**, there has been greater than 95% medication adherence at CPHF.
See the Statistics!

Yes by the evidence for 4 of the Central Prison patients.

- Patient #1, on tx. for 9 months+, so far no SIB.
- Patient #2, on tx. for 9 months+, much less SIB.
- Patient #3, on tx. for 9 months+, 1 episode of SIB.
- Patient #4, stopped after 1 week.

Total episodes [before and after tx.]

12 weeks pre-clozapine: 60 visits to CP urgent care
- 24 visits to outside hospital

12 weeks post-clozapine: 8 visits to CP urgent care
- 3 visits to outside hospital
Statistics for the Other Patients at CPHF

- **Patient #4.** On tx. for 6 months, much less SIB.
- **Patient #5.** On tx. for 3 months, one episode of SIB. (secondary gain?? Such as attention)
- **Patient #6.** On tx. for 3 months, one episode of SIB. (secondary gain??)
- **Patient #7.** On tx. for 2 months. **MUCH better. NO SIB.**
- **Patient #8.** On tx. for 2 months. **Much less SIB.**
## Results of Risky/SIB Behaviors of All Central Prison Patients to Date

<table>
<thead>
<tr>
<th>Risky/SIB Behaviors</th>
<th>Pre-clozapine (12 weeks)</th>
<th>Post-clozapine (12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time Frame of 12 Weeks</td>
<td>12 Weeks Once Treatment</td>
</tr>
<tr>
<td>Urgent Care Visits</td>
<td>92</td>
<td>26</td>
</tr>
<tr>
<td>Outside ED Visits</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Infractions</td>
<td>107</td>
<td>47</td>
</tr>
</tbody>
</table>

WOW..................

North Carolina Department of Public Safety
Statistics!

- 72% decrease in urgent care visits
- 93% decrease in outside ED visits
- 56% decrease in infractions
Positive Results of Risky/SIB Behaviors of All Patients to Date

- 72% decrease in Urgent Care Visits
- 93% decrease in Outside ED Visits
- 56% decrease in infractions

Cost Savings

↓ injury costs  ↓ staff burnout
Conclusion

1. There is a **benefit for many patients**.
2. Many inmate patients are **asking for clozapine for symptom relief** or maybe secondary gain of attention.
3. Dr. Sheitman from UNC reports gratitude with CPHS staff making the **clozapine program a success**.
4. Patients do not want to come off the medication even when discharged or released.
5. Most patients report “**I feel calmer**”.
6. **$$ Savings** of less SIB and hospital encounters.
7. **Monitoring is essential** to the success of treatment and patient safety.
1. True or False

1. Clozapine is the 1st drug of choice for all schizophrenic patients.
1. Answer

False

- Clozapine is for treatment resistant schizophrenia [when 2 or more other antipsychotic medications have not worked] or recurrent suicidal behavior.
2. True or False

2. Clozapine potential side effects and risks are not as important as the benefits of taking this medication.
2. Answer

False

- Potential life threatening risk related to decrease WBC’s and heart failure. [agranulocytosis and myocarditis]
3. True or False

- REMS is an FDA program called Risk Evaluation Mitigation Strategy in which all patients in the U.S.A. prescribed clozapine must be included [registered].
3. Answer

True

This registry reviews patient status for safe administration.
4. True or False

- All responsibility for clozapine treatment & documentation is by psychiatry, psychology and lab.
4. Answer

False

Nursing responsibilities include patient compliance, education, vital signs, EKG, review of labs as well as inform the provider of side effects, delay of lab collection and if a medication dose is missed. 2 missed doses may need for the medication to be restarted with titration.
5. True or False

Pharmacy will fill medication when labs are absent or reports not available.
5. Answer

False !!!!!

No labs...No Medication!
6. True or False

Pharmacy will fill clozapine medication if the ANC is less than 1500 for general population or less than 1000 for BEN [benign ethnic neutropenia].
6. **Answer**

**False**

Pharmacy will notify the provider who will make the decision. Decreased ANC increases the risk of infection and potential inability to fight infection which can result in death.
7. True or False

Clozapine can safely be given with monitoring of labs [WBC & myocarditis panel], EKG, vital signs and side effects.
7. Answer

TRUE!!!!!
Nurse Blue sees Ms. Jones for a cold and headache in Sick Call. Ms. Jones has a temperature of 101. She reports she is ok, but is observed frequently closing her eyes during the exam. When asked, she affirms that she is tired. The medication review includes clozapine and Monistat.
8. What do you do?

A. Call the doctor and ask for an antibiotic order.

B. Provide care for Ms. Jones through Nursing Protocol non-urgent Cold/Cough Flu-like Symptoms: patient education re: Acetaminophen standing order, rest x 2 days and return if not better in 5 days.

C. [Recall patient on clozapine should report flu-like symptoms and lack of energy] Call the provider and SBAR report:

S: flu-like symptoms, lack of energy
B: 46 year old female with MH dx Schizophrenia on clozapine and Monistat
A: Temp. 101
R: Labs [CBC, myocarditis panel] EKG for further assessment.
8. ANSWER

C.

SBAR Report
CEU’s  For Nurses

- Please follow the link
  https://www.surveymonkey.com/r/DPSclozapine
to Survey Monkey for
BON approved questions and
CEU certificate for 1 hour
Reference Pages

- Remember to **click top right button for reference handouts**.
- You will be able to **print the reference handouts**.

*Thank you for providing quality care to our patients!*