An Option for Clozapine Monitoring

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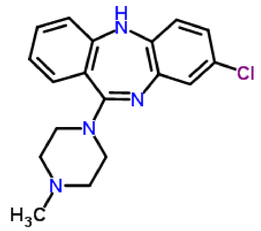


Introduction:

Schizophrenia affects around 1% of the people in the world at some point in their lifetime. Clozapine remains the most effective antipsychotic available today for individuals with schizophrenia who do not respond to first line antipsychotic treatment – it should be third line drug used – or have persistent suicidal ideation or aggressive behavior. However, monitoring remains a significant barrier to prescription and treatment adherence. Data indicates, however, that most patients receive clozapine years after they would be good candidates for it, and many may never receive clozapine at all. Improved access to clozapine could benefit millions of patients and could result in substantial cost savings to the entire health care system. To assist in increasing the usability of Clozapine and improve compliance, there are alternative monitoring options available.

REMS Clozapine Treatment Recommendations and ANC Monitoring Guidelines:

ANC Level	Treatment Recommendation	Frequency ANC Monitoring
Normal Range for New Patient: **General Population** ☐ ANC ≥1500/mm³ **BEN Population** ☐ ANC ≥1000/mm³ ☐ Obtain at least two baseline ANC levels before initiating treatment *Benign Ethnic Neutropenia (BEN)	☐ Initiate treatment ☐ If treatment interrupted: - <30 days, continue monitoring as before - ≥30 days, monitor as if new patient ☐ Discontinuation for reasons other than neutropenia	☐ Weekly from initiation to 6 months ☐ Every 2 weeks from 6 to 12 months ☐ Monthly after 12 months ☐ See Section 2.4 of Prescribing Information
Mild Neutropenia* (1000-1499/mm³)	**General Population:** ☐ Continue Treatment **BEN Population:** ☐ Mild Neutropenia is normal range for BEN population, continue treatment ☐ Obtain at least two baseline ANC levels before initiating treatment ☐ If treatment interrupted: - <30 days, continue monitoring as before - ≥30 days, monitor as if new patient ☐ Discontinuation for reasons other than neutropenia	**General Population:** ☐ Three times weekly until ANC ≥1500/mm³ ☐ Once ANC ≥1500/mm³, return to patient's last "Normal Range" ANC monitoring interval**† **BEN Population:** ☐ Weekly from initiation to 6 months ☐ Every 2 weeks from 6 to 12 months ☐ Monthly after 12 months ☐ See Section 2.4 of Prescribing Information
Moderate Neutropenia* (500 – 999/mm³)	**General Population:** ☐ Recommend hematology consultation ☐ Interrupt treatment for suspected clozapine induced neutropenia ☐ Resume treatment once ANC normalizes to ≥1000/mm³ **BEN Population:** ☐ Recommend hematology consultation ☐ Continue treatment	**General Population:** ☐ Daily until ANC ≥1000/mm³ then ☐ Three times weekly until; ≥1500/mm³ ☐ Once ANC ≥1000/mm³, check ANC weekly for 4 weeks then return to patient's last "Normal Range" ANC monitoring interval** **BEN Population:** ☐ Three times weekly until; ≥1000/mm³ or ≥ patient's known baseline ☐ Once ANC ≥1000/mm³ or patient's baseline, check ANC weekly for 4 weeks then return to patient's last "Normal BEN Range" ANC monitoring interval**
Severe Neutropenia* (>500/mm³)	**General Population:** ☐ Recommend hematology consultation ☐ Interrupt treatment for suspected clozapine induced neutropenia ☐ Do not rechallenge unless prescriber determines benefits outweigh risks **BEN Population:** ☐ Recommend hematology consultation ☐ Interrupt treatment for suspected clozapine induced neutropenia ☐ Do not rechallenge unless prescriber determines benefits outweigh risks	**General Population:** ☐ Daily until ANC ; ≥1000/mm³ ☐ Three times week until; ≥1500/mm³ ☐ If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/mm³ **BEN Population:** ☐ Daily until ANC ; ≥500/mm³ ☐ Three times week until ANC; ≥ patient's established baseline ☐ If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/mm³ or at patient's baseline

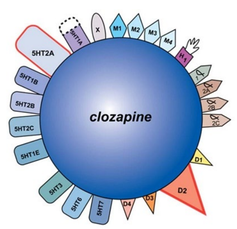
Abstract:

Despite having been in use for over 60 years, Clozapine is often overlooked as a potential source of severe side effects and due to the need for constant and continuous monitoring. Alternative monitoring options may be a way to increase provider and patient comfort around the usage of Clozapine.

Discussion:

Several anonymous surveys were given to prescribers to identify and rank the importance of barriers to Clozapine use and identify potential solutions [4, 5]. The need for close monitoring, regular blood work, and potential for non-adherence to blood work, the highest concern overall, were reported as the greatest clinical barriers. Solutions surveys found that point of care fingerstick [4] and among nine solutions, the ability to obtain lab results in the physician's office or pharmacy was top ranked. [5]

Severe neutropenia (ANC <500/μL) due to clozapine is well documented, leading to serious infections and even death in about 0.8% (or less) of patients treated. The required weekly ANC monitoring for 6 months places a large burden on patients, caregivers, and clinical staff, contributing to lower drug utilization rates and patient non-adherence. There are several Point-of-care testing (POCT) devices that are FDA approved to measure total white blood cell counts and differential counts in capillary or venous whole blood using a finger prick method. Portable mass spectrometry devices, lab-on-a-chip (LOC) and smartphone applications (apps), can return results in less than 15 min from a single drop of blood. [10] White blood cell count correlation between the POCT device and routine laboratory methods in measuring WBC and neutrophil counts in venous samples being 0.95-0.99. [7, 8]



Correlation between capillary samples using the device and routine methods (venous sample) was 0.77 and 0.82 for WBCs and neutrophils, respectively. [7] Another study for capillary sample versus venous without a POCT device showed 0.99 and 0.82 for WBCs and neutrophils, respectively. [11] Another study by *Schalk et al*.[12] which studied 447 blood samples found no difference in the ANC between the two sample sets.

A study to determine whether fingerprick blood and plasma clozapine levels were equivalent to arm venipuncture blood and plasma levels for the purpose of therapeutic monitoring found that a fingerprick blood sample of 50 micro L was sufficient to measure clozapine levels accurately at steady state. [6]

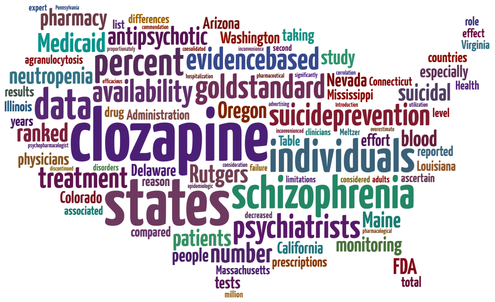
A randomized cross-over trial have shown that consistent favoring of capillary blood testing as a significant number of patients reported less pain and anxiety, greater convenience, less fear, and a better understanding of the intended purpose of sample collection. [8] There have been several FDA approved POCT devices which can return results within 5 minutes and some have the ability to deposit ANC results automatically into the REMS system.

My project has been creating a process to utilize fingerprick blood Clozapine levels and to monitor ANC levels. This can be done in the hospital or outpatient setting as follows:

To obtain a capillary ANC and/or a CBC with diff

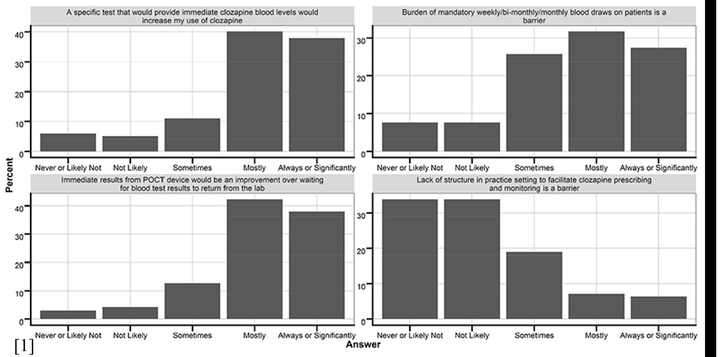
1. Get a microtainer with a purple/lavender capillary tube
2. Obtain blood sample
3. Create a text blood order in Epic
4. Send sample to 911 tube station

Of note, this is the procedure for in hospital testing at this time.



My project has been creating a process to utilize finger-prick blood Clozapine levels and to monitor ANC levels. By having portable, less painful, intrusive method for gathering both Clozapine levels and ANCs, we could increase patient outcomes by improving compliance with Clozapine treatment as well as increasing the likelihood that providers would utilize Clozapine as a treatment option. As finger-prick samples can be done by nursing in the patient's home this could increase patient safety during long-term monitoring.

Further study needs to be done on our laboratory result reliability and consistency. It is possible that as venous CBC and differentials are slightly more reliable, using finger-prick monitoring method may be an option to monitor remotely with changes to the CBC being the call to get a venous sample.



[1]

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