Clozapine: Overcoming The Barriers To Increase Use

Frederick C. Nucifora Jr. Ph.D., D.O., M.H.S.
Associate Professor
Director, Adult Schizophrenia Clinic
Director, Clozapine Clinic
Director, Laboratory of Neurobiochemistry
Co-Director Schizoaffective Disorder Precision Medicine Center of Excellence
Dept. of Psychiatry, Johns Hopkins University School of Medicine

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Disclosures

- American Psychiatric Association- Consultant (Clozapine Center of Excellence SMI Adviser)
- Newron Pharmaceuticals- Consultant
- I will discuss off label uses of clozapine.

Objectives

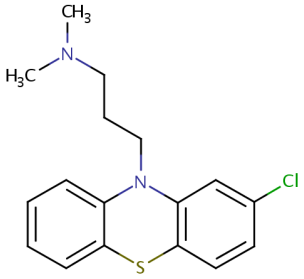
1) To understand clozapine's role in treatment resistant schizophrenia.

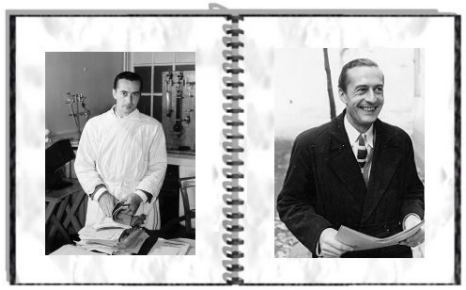
2) To identify the barriers to clozapine use.

3) To learn how to overcome the barriers related to clozapine use.

History of Antipsychotic Development

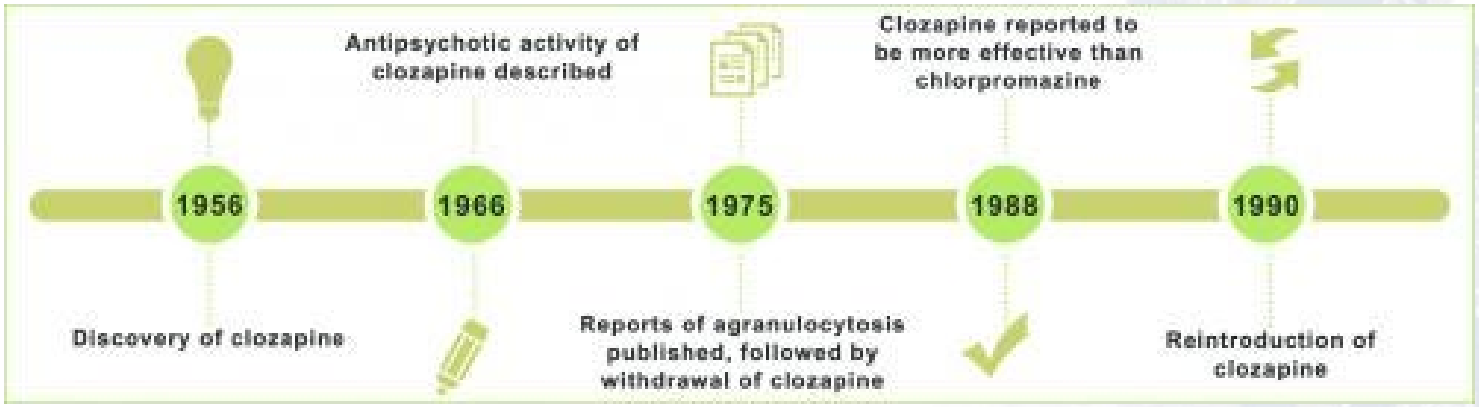
- Chlorpromazine (Thorazine): first antipsychotic
  - Synthesized as an antihistamine for anesthesia (1950)
  - French surgeon Henri Laborit noticed unusual calming properties
  - Psychiatrist Heinz Lehmann began chlorpromazine clinical trials
  - Chlorpromazine was approved by the FDA in1954





- Development of other “typical” agents – late 1950s to mid-1970s
  - Based on chemical structure or effect on movement in rats
  - Similar efficacies and side effect profile

Discovery of Clozapine



Bryan, 2014

Clozapine

INDICATIONS

Treatment resistant schizophrenia or schizoaffective disorder

Reduction in the risk of recurrent suicidal behavior in schizophrenia and schizoaffective disorders

Reduction in the risk of causing tardive dyskinesia, EPS, and akathisia

Defining Treatment Response Categories

~ 70% of patients respond to treatment with standard antipsychotics termed non-treatment resistant schizophrenia **(non-TRS)**

~30% of patients have treatment resistant schizophrenia **(TRS)**

The only FDA approved medicine for TRS is clozapine

~30% of TRS patients do not respond to clozapine, termed ultra-treatment resistant schizophrenia **(UTRS)**

~ 800,000 individuals with TRS

Consensus Criteria for TRS

Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology

Prior Treatment	Treatment Duration	Severity	Adherence
≥2 past adequate treatment episodes with different antipsychotics	≥6 weeks at therapeutic dose	At least moderate disease severity, <20% symptom reduction prospectively, at least moderate functional impairment based on a validated scale	≥ 80% of prescribed doses taken Adherence should be assessed using at least two sources

Howes OD, et al., Am J Psychiatry. 2017

Three key elements define the concept of TRS.
1) Confirmed diagnosis based on validated criteria
2) Adequate pharmacological treatment
3) Persistence of significant symptoms

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Landmark Clozapine Study

Kane J, Honigfeld G, Singer J, Meltzer H Y. Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch. Gen. Psychiatry. 1988;45:789–796

In 1988, multicenter clinical trial to assess clozapine's efficacy in refractory patients

Single-blind trial of haloperidol (mean dosage, 61 +/- 14 mg/d) for six weeks

286 non-responders were then randomly assigned to clozapine or chlorpromazine for six weeks

Responders: 30% clozapine compared to 4% chlorpromazine

Significantly greater improvement:

- Brief Psychiatric Rating Scale
- Clinical Global Impression Scale

Included negative as well as positive symptoms

Clozapine is superior to all other antipsychotics in the US

1) Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) investigation Phase 2: *Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients who did not respond to prior atypical antipsychotic treatment*

Time until treatment discontinuation for any reason was significantly longer for clozapine than for quetiapine or risperidone, but not for olanzapine.

Time to discontinuation because of inadequate therapeutic effect was significantly longer for clozapine than for olanzapine, quetiapine, or risperidone.

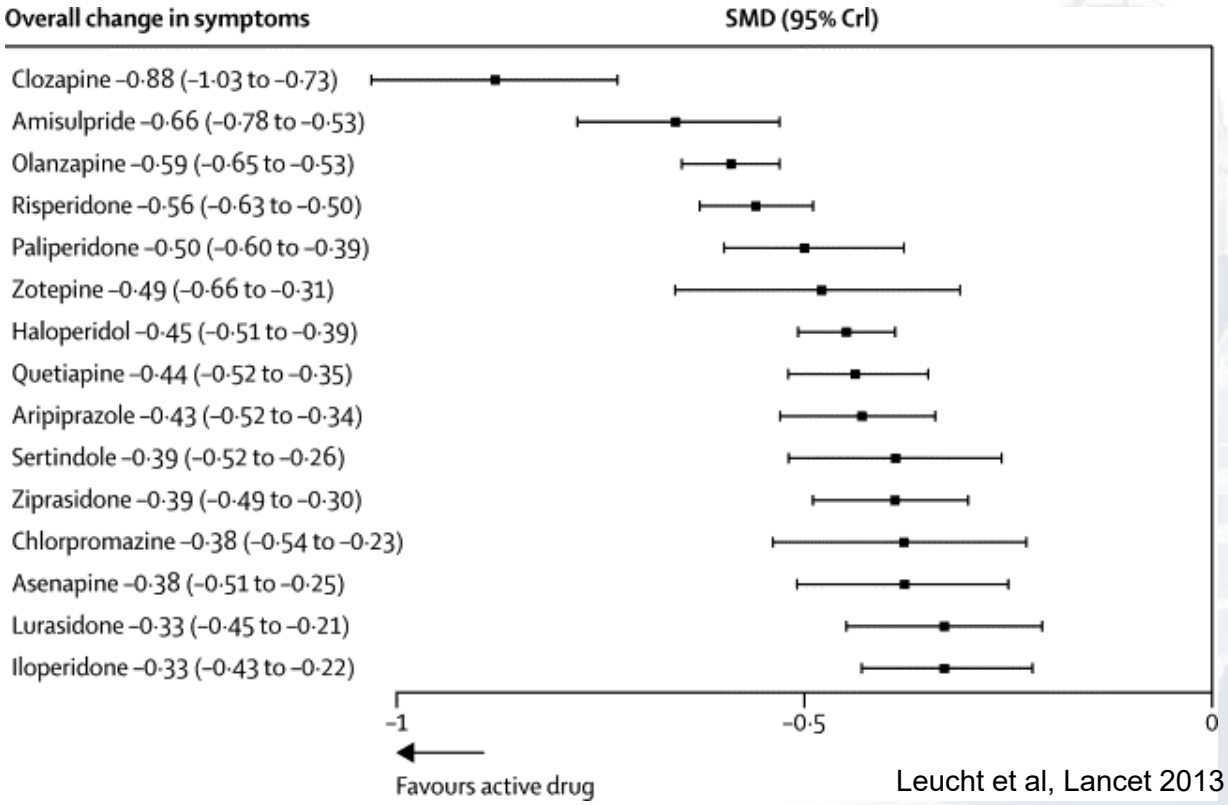
At 3-month PANSS total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone, but not olanzapine.

2) Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study

28% of clozapine patients achieved remission, after failure on amisulpride and/or olanzapine.

Clozapine should be used after patients fail a single antipsychotic trial

Clozapine is superior to all other antipsychotics in the US



Leucht et al, Lancet 2013

Mean reduction in PANSS of 22 points

26% reduction in PANSS from baseline

Siskind et al *Can J Psychiatry* 2017, Lieberman JA, et al.. *N Engl J Med*. 2005;353:1209–23; Lewis SW, et al. *Schizophr Bull*. 2006;32(4):715–23

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Clozapine is Protective Against Suicide

Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT)

	Clozapine group (n = 490)	Olanzapine group (n = 490)	p-value (95% CI)
Patients with end points, total	102 (20.8)	141 (28.8)	0.005 (0.03–0.13)
Patients with significant suicide attempts[§]	34 (6.9)	55 (11.2)	0.03 (0.01–0.08)
Patients with hospitalizations to prevent suicide[§]	82 (16.7)	107 (21.8)	0.05 (0.00–0.10)
Patients showing much 'worsening from baseline' on the CGI-SS[§§]	120 (24.5)	161 (32.9)	0.005 (0.03–0.14)
Suicide deaths[§ and §§]	5 (1.0)	3 (0.6)	0.73 (-0.02–0.01)
All rescue interventions to prevent suicide	118 (24.1)	155 (31.6)	0.01 (0.02–0.13)

Meltzer, H. Y. et al., *Archives of general psychiatry*, 2003

The Protective Effect of Clozapine on Suicide: A Population Mortality Study of Statewide Autopsy Records in Maryland

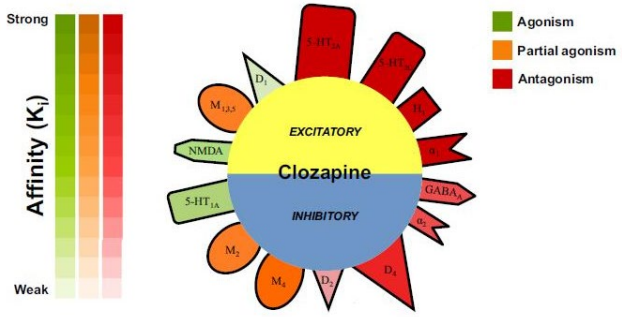
Table 2. Manner of Death of Decedents With Olanzapine and Clozapine Detected on Autopsy[a]

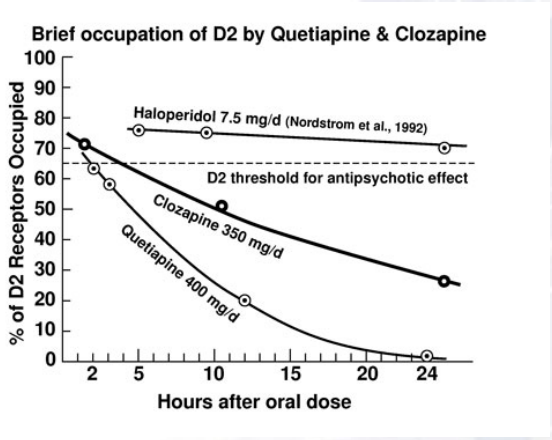
Manner of Death	Olanzapine (n=571)	Clozapine (n=50)	Total (n=621)
Accident	163 (29)	23 (46)	186 (30)
Likely suicide	408 (71)	27 (54)	435 (70)

[a]Values are shown as n (%). Decedents with clozapine were significantly less likely to have died by suicide than by accident compared to those with olanzapine: odds ratio = 0.47; 95% CI, 0.26–0.84; *P* = .011.

Lee, B. J., Cotes, R. O., Mojtabai, R., Margolis, R. L., Nucifora, F. C., & Nestadt, P. S. (2023). *The Journal of clinical psychiatry*

Reduced Risk of Tardive Dyskinesia





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Clozapine Side Effects: Life Threatening

Severe Neutropenia (previously Agranulocytosis) (0.05-0.86%):

ANC less then 500/ul

Myocarditis (0.015-8.5%):

87% occur with in the first 4 weeks of initiating treatment

Up to a 50% mortality rate

Pulmonary Embolism:

Increased risk of venous thromboembolic events

Mortality rate of a clotting complication while on clozapine was 36%

Seizures (1-3%):

Dose dependent risk

Constipation (15-60%):

Intestinal obstruction, fecal impaction, and paralytic ileus are rare but mortality rate can be as high as 20% for severe constipation

Clozapine Side Effects

Metabolic syndrome

Eosinophilia

Hypersalivation: treatment limiting – stigmatizing and hinders sleeping

Orthostatic hypotension: ~ 9% of patients, usually occurs early in treatment

Tachycardia: ~ 25% of patients, rarely of clinical significance

Sweating

Sedation: ~50% of patients, particularly during the initiation of treatment

Urinary incontinence

OCD

The Clozapine REMS (Risk Evaluation and Mitigation Strategy)

FDA-mandated to help ensure patient safety

Single patient registry with specific requirements

The goal is to mitigate the risk of severe neutropenia

The Clozapine REMS (Risk Evaluation and Mitigation Strategy)

To minimize the risk of severe neutropenia associated with the use of clozapine, the Clozapine REMS Program includes the following key program requirements:

Prescribers

- Must certify in the Clozapine REMS Program to prescribe clozapine
- Must enroll all patients in the Clozapine REMS Program
- Must report patient ANC to the Clozapine REMS Program for every prescription of clozapine

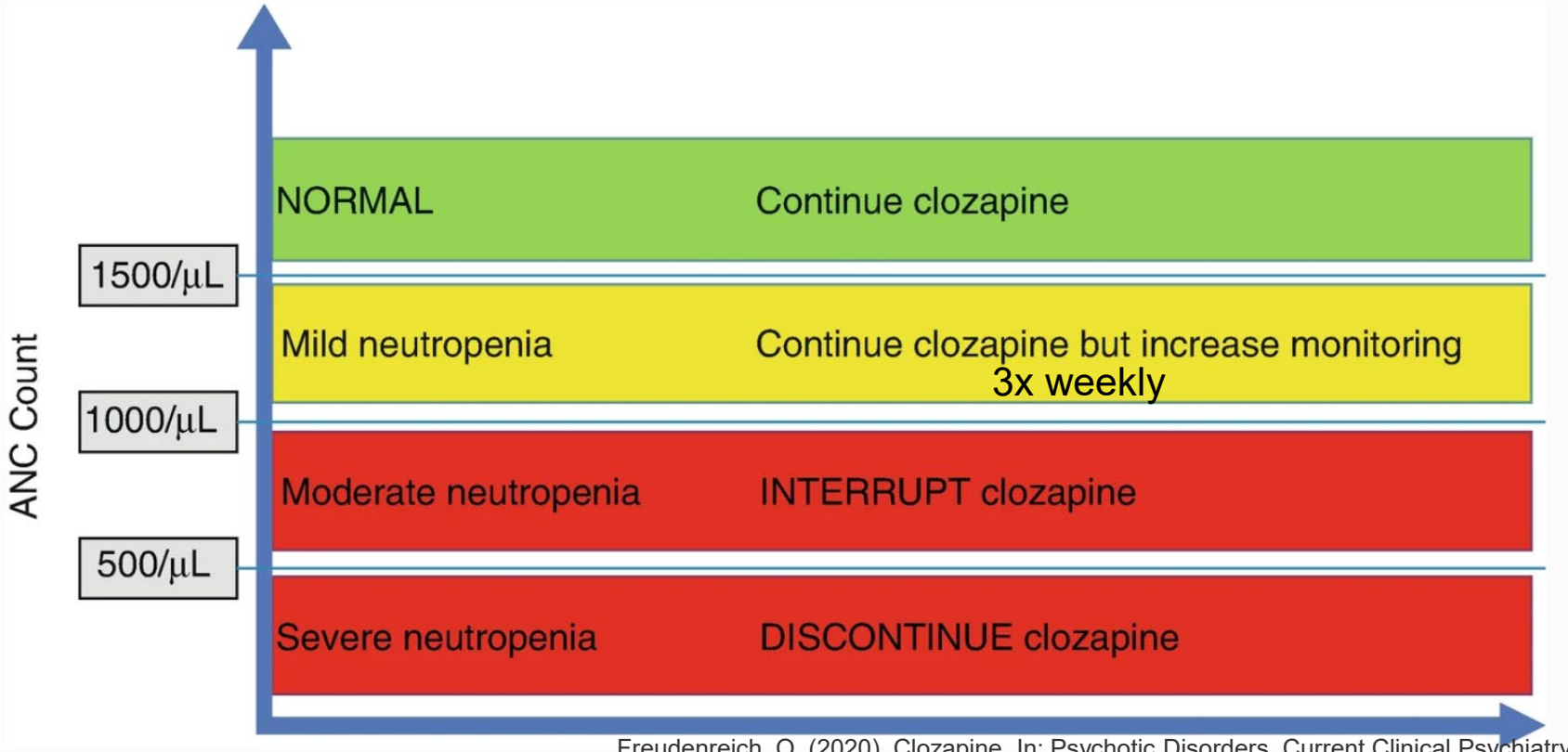
Pharmacies

- Must certify in the Clozapine REMS Program to dispense clozapine. This includes both inpatient and outpatient pharmacies
- Must verify the prescriber is certified and the patient is enrolled, prior to dispensing clozapine
- Must verify ANC is current and acceptable for each patient, or the prescriber authorized the continuation of clozapine treatment by providing the treatment rationale, prior to dispensing clozapine

Patients

- Must be enrolled in the Clozapine REMS Program by the prescriber to receive clozapine
- Must comply with the ANC testing requirements

The Clozapine REMS: ANC Monitoring



Freudenreich, O. (2020). Clozapine. In: Psychotic Disorders. Current Clinical Psychiatry.

Weekly from initiation to 6 months, every 2 weeks from 6 to 12 months, monthly after 12 months

BEN 500/uL less per category

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Clozapine is Underutilized In the U.S.

At least 30% should be treated with clozapine.

Only 4.4% of patients are on clozapine in the U.S.

About 10% of FEP fulfill this definition after a year.

68% of patient have 3 or greater trials before clozapine initiation and mean time to prescribing is 8 years

In patients who already failed 2 adequate trials, there is a 48 month delay in clozapine use with an average of 5 prior trials.

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Howes OD, et al. *Br J of Psychiatry* 2012;201:481-5; Alessi-Severini S, et al. *PLoS ONE* 2014; Nielsen J, et al. *European Neuropsychopharmacology* 2012;22:818-824; Gören JL, et al. *Psychiatric Servi*2013;64:527-33; Gallego JA, et al. *Schizophr Res* 2012;138:18-28

Barriers to Clozapine Use

Barriers related to:

1) **Medication**
   - Side effects

2) **Patients**
   - Blood Draws (often cited as the most significant barrier)
     - Frequent blood draws
     - Concern for adherence to blood draws
   - Benign Ethnic Neutropenia
   - Inpatient hospitalization for initiation

3) **Clinicians**
   - Physician concern for risk of serious side effects and that patients will be unhappy with side effects and blood draws
   - Lack of knowledge or experience and inability to provide adequate monitoring of patients for initiation and maintenance.

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Barriers to Clozapine Use

4) Health system

Clozapine Risk Evaluation and Mitigation Strategy (REMS)
- Administrative complexities and time consuming
- Difficulty with transition of care

Lack of centralized resources for coordinating services
- Family and patient education
- Laboratory
- Medical consultation
- Adherence monitoring
- Case management

General Barriers
- Lack of standardized materials for shared decision making
- Lack of protocols for treatment initiation, monitoring and management of side effects
- Lack of resources for help
- Pharmacy and formulary issues
- Transportation issues for appointments and blood draws

Reasons to Overcome the Barriers

Superior efficacy

Reduced Suicidality

Lower risk of movement disorders

Polypharmacy has medical risks

Decreased discontinuation

Decreased Mortality

- 44% lower compared to other antipsychotics
- Clozapine lowers the odds of all physical health events

Overall cost savings to health care system/decreased hospitalizations

- ~$20,000 per patient within the first year

Potential improvement in real world functionality

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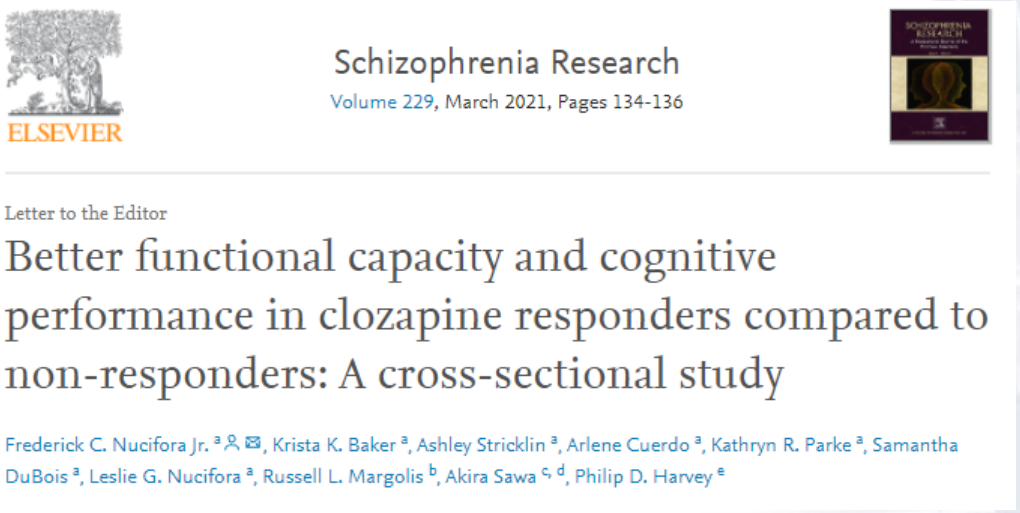
Vanasse A, et al.. *Acta Psychiatrica Scandinavica* 2016; 134, 374–384; Vermeulen JM, et al. *Schizophrenia Bulletin* 2019; 45(2): 315–329.
Velligan, et al. *Psychiatric Services* 2015;66(2):127-33; Goren et al *Psychiatric Services* 2016

Clozapine Response, Functional Capacity and Cognitive Performance



ELSEVIER

Schizophrenia Research
Volume 229, March 2021, Pages 134-136

Letter to the Editor

Better functional capacity and cognitive performance in clozapine responders compared to non-responders: A cross-sectional study

Frederick C. Nucifora Jr. [a], Krista K. Baker [a], Ashley Stricklin [a], Arlene Cuerdo [a], Kathryn R. Parke [a], Samantha DuBois [a], Leslie G. Nucifora [a], Russell L. Margolis [b], Akira Sawa [c, d], Philip D. Harvey [e]

Question: Does response to clozapine improve functional capacity and cognitive performance.

Utilizing simulations of real-world tasks critical for life functioning

Comparing clozapine responders to non-responders

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Clozapine Response, Functional Capacity and Cognitive Performance: Methods

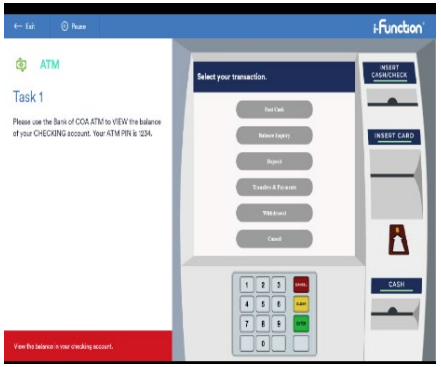
27 patients with treatment refractory schizophrenia (TRS) and currently on clozapine, ages 21 to 72 were enrolled in the study.

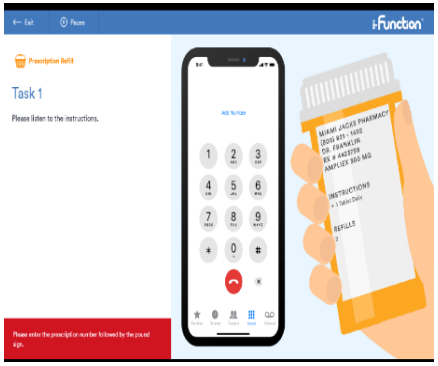
Clozapine levels above 350ng/ml.

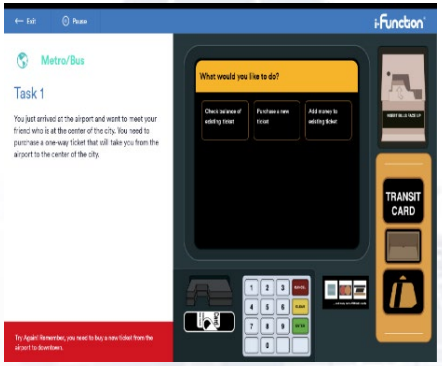
A patient was considered a responder if their total PANSS score was less than 58.

18 patients were considered responders and 9 patients non-responders

Clozapine Response, Functional Capacity and Cognitive Performance







Miami Computer-Based Functional Assessment System
1) ATM
2) Medication refill
3) Ticket purchase

Brief Assessment of Cognition in Schizophrenia (BACS)

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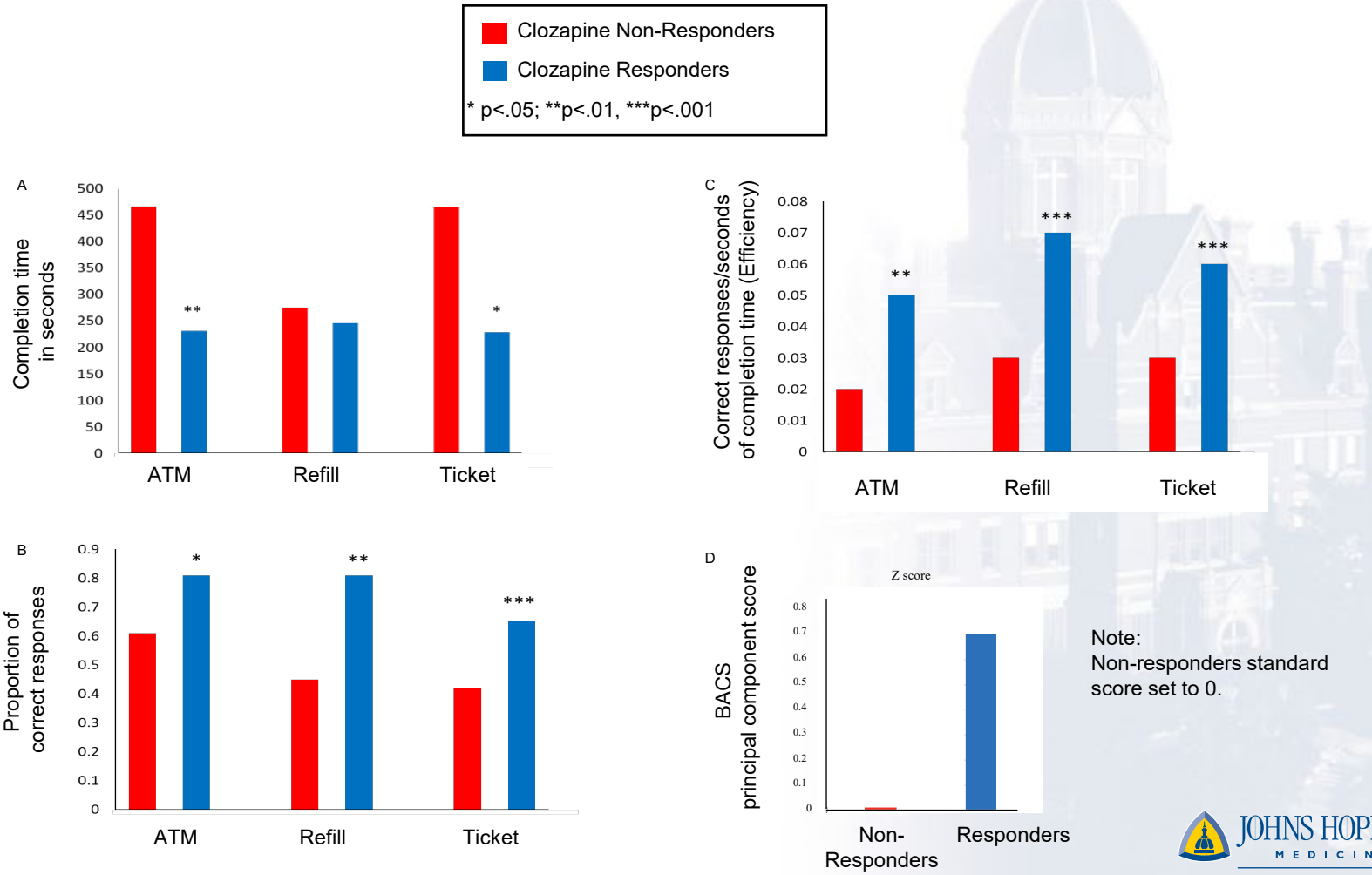
Improved Functional Capacity and Cognitive Performance in Clozapine Responders Compared to Clozapine Non-responders



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Clozapine Response, Functional Capacity and Cognitive Performance: Summary and Implications

Clozapine responders perform better on cognitive and functional capacity assessments.

This further supports the use of clozapine in patients with TRS not only for greater symptom relief but also for improved real world functioning.

Overcoming the Barriers

Barriers related to the **medication** can be monitored and/or mitigated:

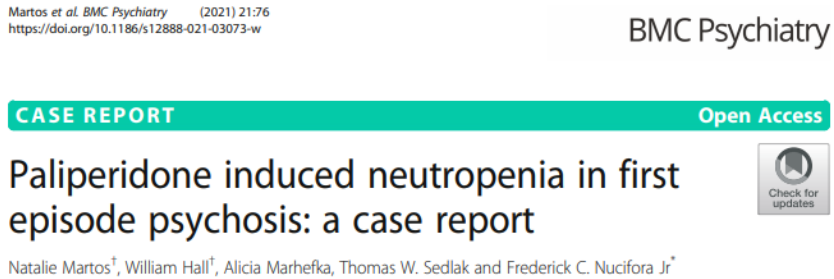
Side effects

Severe neutropenia- follow ANC

Myocarditis- follow cardiac labs

Seizures- antiseizure medications

Constipation- bowel regimens

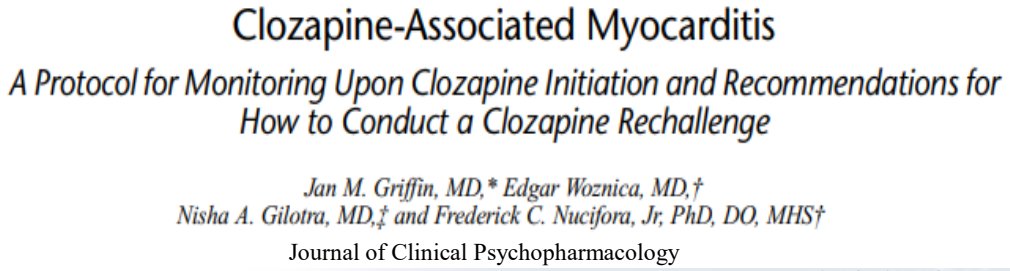

Martos et al. BMC Psychiatry (2021) 21:76
https://doi.org/10.1186/s12888-021-03073-w

BMC Psychiatry

CASE REPORT Open Access

Paliperidone induced neutropenia in first episode psychosis: a case report

Natalie Martos†, William Hall†, Alicia Marhefka, Thomas W. Sedlak and Frederick C. Nucifora Jr*


Clozapine-Associated Myocarditis

A Protocol for Monitoring Upon Clozapine Initiation and Recommendations for How to Conduct a Clozapine Rechallenge

Jan M. Griffin, MD,* Edgar Woznica, MD,† Nisha A. Gilotra, MD,‡ and Frederick C. Nucifora, Jr, PhD, DO, MHS†

Journal of Clinical Psychopharmacology

Overcoming the Barriers

Barriers related to **patients** can be addressed:

Blood Draws
Case management/“wrap around” services
Point of care services

BEN
Improved guidelines and understanding

Inpatient hospitalization for initiation
Protocols to initiate clozapine in the outpatient setting

Overcoming the Barriers

Barriers related to **clinicians** can be overcome:

Physician concern for risk of serious side effects and that patients will be unhappy with side effects and blood draws

Clinicians perceive that patients will not comply with treatment

Largely misperceptions

Overcoming the Barriers

Physicians overestimate the frequency of side effects especially severe neutropenia

Psychiatrist vs patient attitudes towards clozapine
30% of psychiatrists rated clozapine as the drug of choice compared to 85% of patients

52% of psychiatrists thought patients were unhappy about blood draws compared to 19% of patients.

Patient attitudes towards clozapine
In a study of 1284 patients from 27 clozapine clinics in UK

- 86% feel better on clozapine
- 89% prefer clozapine to other antipsychotics
- 87% think advantages outweigh disadvantages
- 28% rank frequent blood work as biggest disadvantage

Nielsen J, et al. Psychiatrist's attitude towards and knowledge of clozapine treatment. *J Psychopharmacol* 2010;24:965-71. Hodge K and Jesperson S. Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians. *Int J Mental Health Nurs* 2008;17:2-8, Taylor et al. Clozapine- a survey of patient perspectives. *Psychiatr Bull* 2000;24:450-2

Overcoming the Barriers

Barriers related to **clinicians** can be overcome:

Lack of knowledge or experience utilizing clozapine and identifying appropriate patients for clozapine

Incorporating clozapine education into residency programs including clinic time.

Specialized courses related to Clozapine use for practicing clinicians.

Freudenrich et al. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. *Acad Psychiatry* 2013; 37:27-30. Falzer PR, et al. Optimizing clozapine through clinical decision making, *Acta Psychiatr Scand* 2012;126:47-58.

Overcoming the Barriers

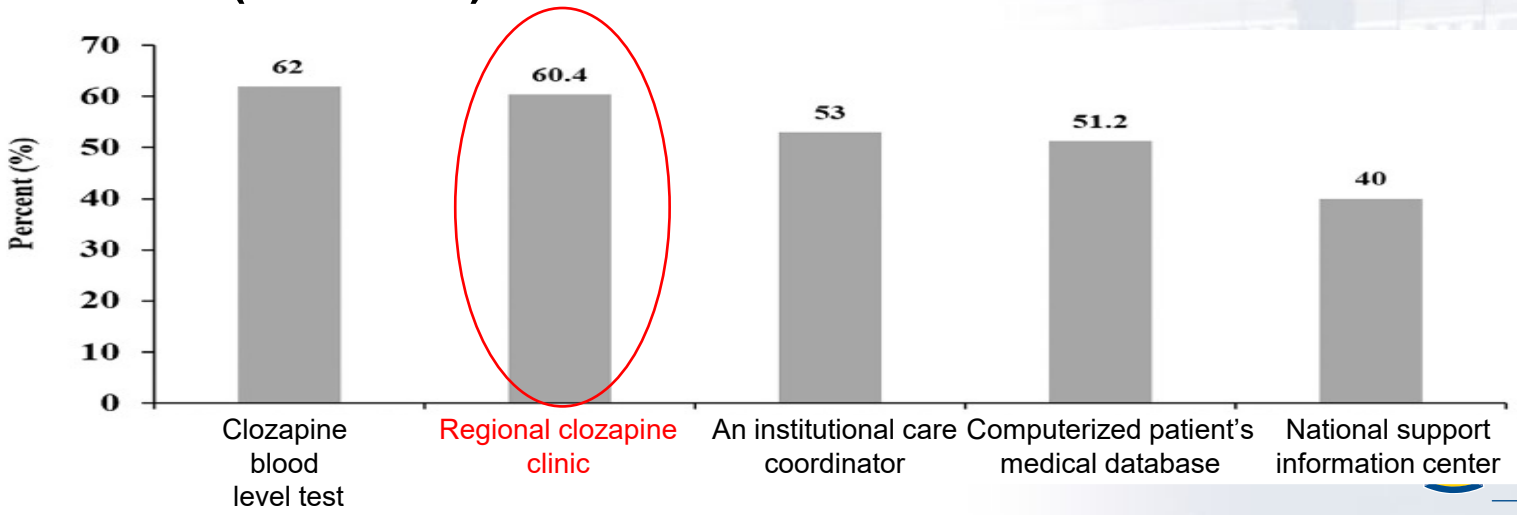
Barriers related to **Health Systems** can be surmounted:

Clozapine Risk Evaluation and Mitigation Strategy (REMS)

Lack of centralized resources for coordinating services

General barriers

Inability to provide adequate monitoring of patients for initiation and maintenance (Clinician)



Factors encouraging clinicians to initiate clozapine

Daod et al. Psychiatrists' attitude towards the use of clozapine in the treatment of refractory schizophrenia: A nationwide survey. Psychiatry Res. 2019 May;275:155-161. doi: 10.1016/j.psychres.2019.03.029.

Identifying Clozapine Candidates: High Suspicion

Clinical factors that may predict TRS (high suspicion)

- Younger age of onset
- First degree or second degree relatives with schizophrenia
- Longer duration of untreated psychosis
- Negative symptoms
- Lower premorbid functioning
- Failure of one antipsychotic
- Sum of three baseline PANSS items - conceptual disorganization (P2), difficulty in abstract thinking (N5), and unusual thought content (G9).

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Wimberley T et al. *Lancet Psychiatry*. 2016;3(4):358-366; Demjaha A, et al. *Psychol Med*. 2017;47(11):1981-1989; Bozzatello et al. Frontiers in Psychiatry 2019; Ortiz BB, et al. *Schizophr Res*. 2020;218:195-200; Dempster K, et al. J Pers Med. 2021 Jul 24;11(8):711; Chan SKW et al. *Schizophr Bull*. 2021;47(2):485-494; Correll CU et al. *CNS Drugs*. 2022;36(7):659-679. doi:10.1007/s40263-022-00932-2

Identifying Clozapine Candidates: High Priority Starts

1) Failure of two antipsychotics

2) Suicidality

3) Tardive Dyskinesia

<u>Potential off label uses (all with supportive data):</u>

- Treatment Resistant BPAD
- Psychotic Depression
- Borderline Personality Disorder
- Violent Patients
- Substance Use Disorder
- Psychosis in Parkinson's Disease

Summary

Clozapine is vastly underutilized in the U.S.

Delay of initiating clozapine treatment is associated with poorer outcomes.

Clozapine use leads to reduced morbidity and mortality.

At least 30% of patients should be on clozapine (failure of other meds, suicide, low risk of movement disorders).

Clozapine should be initiated after two adequate treatment failures.

Clozapine side effects can be monitored and mitigated.

Data suggest that patients are less bothered by blood draws than prescribers tend to think and prefer clozapine to other medications.

Clozapine Consultation Clinic at Johns Hopkins

- **One-time, second-opinion evaluation for patients who may benefit from clozapine**

Allison S. Brandt, M.D.
Russell L. Margolis, M.D.
Frederick C. Nucifora, Jr, D.O., Ph.D., M.H.S.

- Example consult questions:
  1. Would clozapine be a reasonable medication choice for my patient?
  2. I have recommended that my patient start clozapine, but they are reluctant. The consultation may be valuable in their decision making.
  3. My patient tried clozapine, but experienced some side effects. Can we safely try this medication again?

- If clozapine recommended, referring psychiatrist will receive advice around:
  - Initiation of clozapine
  - Management of adverse effects
  - Administrative requirements

Contact:
psychiatryconsultation@jhu.edu
410-614-3307

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Other Resources

The Clozapine Clinic at Johns Hopkins Bayview Medical Center

Contact:
Arlene Cuerdo
acuerdo1@jhmi.edu
410-550-5689

Clozapine CHAMPION (Center for Help and Assistance for Maryland Prescribers – Intervention Outcomes Network) Consultation Hotline

APA SMI Advisor group national hotline for consultations (Clozapine Center of Excellence)

https://smiadviser.org/submit-consult

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