



New England (HHS Region 1)

MHTTC

Mental Health Technology Transfer Center Network

Funded by Substance Abuse and Mental Health Services Administration

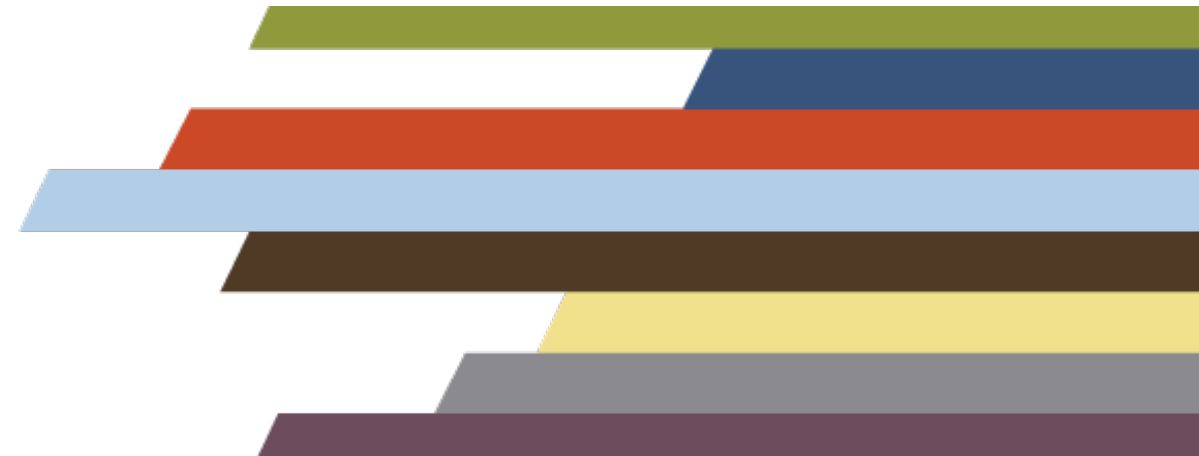
Clozapine

Matcheri Keshavan, MD

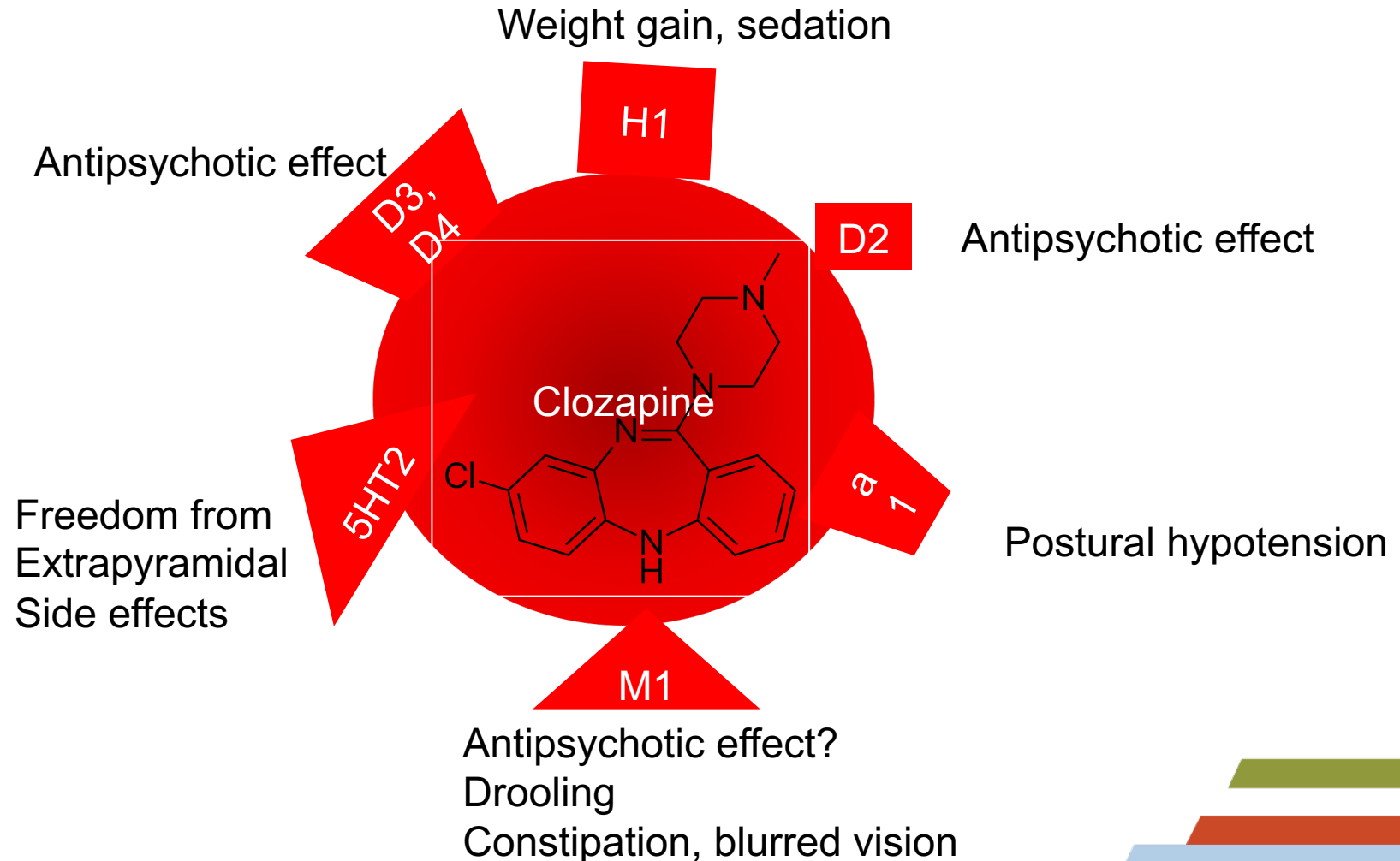
James Feldman, MD, MPH

Clozapine Psychopharmacology Consultation Line

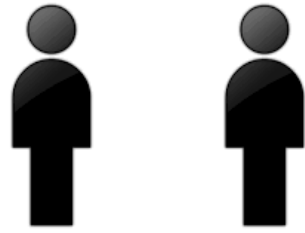
April 15th, 2020



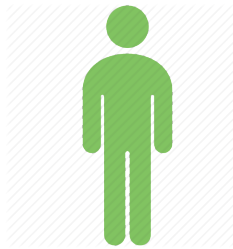
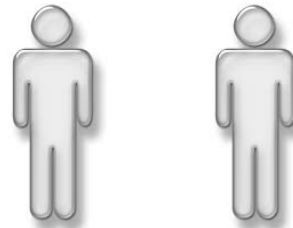
Clozapine Mechanism



CLOZAPINE RESPONSE



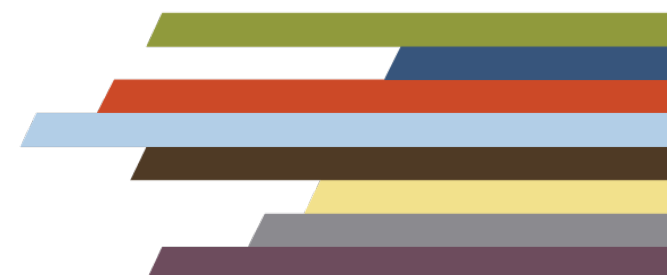
About a third of schizophrenia patients
Do not respond to conventional
antipsychotics (typical or atypical)



About a third of schizophrenia patients
Do not respond to clozapine



? ECT ?? Addition of D2 blocker



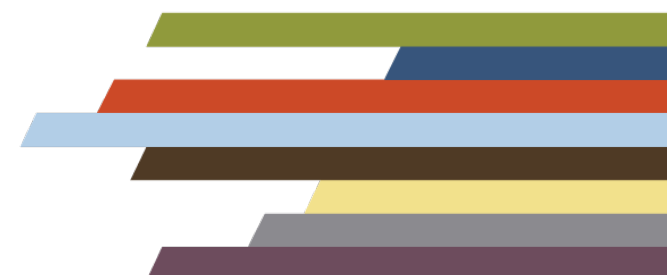
INDICATIONS

Schizophrenia or schizoaffective disorder

- Partially or fully resistant to treatment with other antipsychotic drugs
- Accompanied by persistent suicidal or self-injurious behavior
- Sensitivity to extrapyramidal side effects and patients with tardive dyskinesia

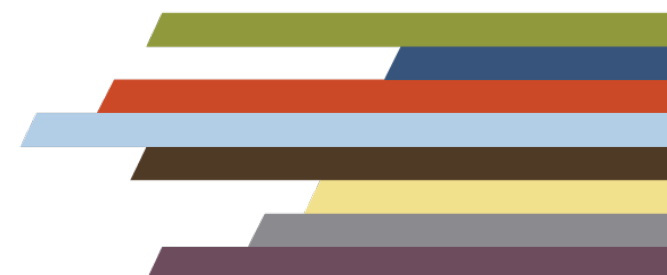
CONTRAINDICATIONS

- Neutropenia
- Cardiac disease
- Seizures



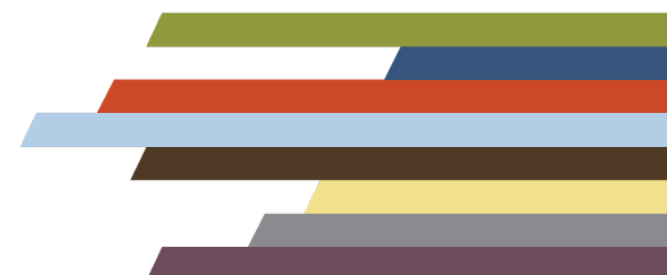
PRE-TREATMENT ASSESSMENT

- Complete blood count
- Weight and height (body mass index), waist circumference, fasting blood sugar (or HbA1c), and fasting lipids.
- Drug levels for patients on anticonvulsant drugs
- Vital signs
- ECG
- An Abnormal Involuntary Movement Scale documenting absence or presence of abnormal motor movements
- Pregnancy test in women of childbearing age



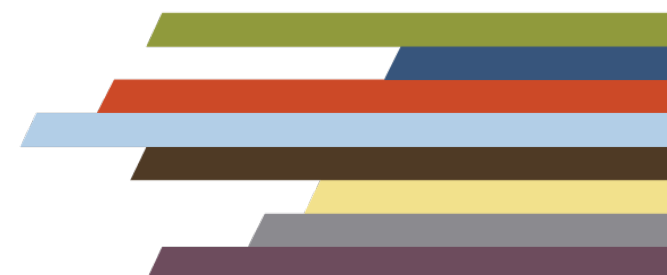
CLOZAPINE MONITORING

- For all patients taking clozapine in the United States, the US Food and Drug Administration requires regular monitoring and registry reporting of neutrophil counts.
- Since 2015 a single registry (**Clozapine Risk Evaluation and Mitigation Strategy [REMS]** Program, <https://www.clozapinerems.com/>).
- REMS requires clinicians to be registered and competent to prescribe clozapine (ie, pass a knowledge test).
 - Pharmacies also need to be certified if they dispense clozapine.
- Patient must be entered into this registry and undergo ANC monitoring as long as a patient receives clozapine (“No blood, no drug”).



CLOZAPINE MONITORING (CONTD)

- Routine neutrophil monitoring is performed at the following intervals:
 - Weekly for first six months
 - 2 weeks for the second six months
 - Every 4 weeks after one year, for the duration of treatment
- If neutropenia develops:
 - **Mild neutropenia** (ANC: 1000 to 1499/microL) – Continue treatment but increase monitoring frequency to three times per week.
 - **Moderate neutropenia** (ANC: 500 to 999/microL) – Interrupt [clozapine](#) treatment, increase monitoring to daily until ANC is 1000/microL at which point clozapine can be reinstituted.
 - **Severe neutropenia/agranulocytosis** (ANC: <500/microL) – Discontinue [clozapine](#). Rechallenge should only occur if the benefits outweigh the risks, in consultation with hematology.



CLOZAPINE REMS

The Single Shared System for Clozapine No Blood, No Drug™

Recommended Monitoring Frequency and Clinical Decisions by ANC Level

ANC Level	Treatment Recommendation	ANC Monitoring
Normal Range for a New Patient <ul style="list-style-type: none">General Population (ANC ≥ 1500/μL) BEN POPULATION <ul style="list-style-type: none">BEN Population (ANC ≥ 1,000/μL)Obtain at least two baseline ANC levels before initiating treatment	<ul style="list-style-type: none">Initiate treatmentIf treatment interrupted:<ul style="list-style-type: none">< 30 days, continue monitoring as before≥ 30 days, monitor as if new patientDiscontinuation for reasons other than neutropenia	<ul style="list-style-type: none">Weekly from initiation to 6 monthsEvery 2 weeks from 6 to 12 monthsMonthly after 12 months <ul style="list-style-type: none">See Section 2.4 of the full Prescribing Information
Mild Neutropenia (1000 to 1499/μL)*	GENERAL POPULATION <ul style="list-style-type: none">Continue treatment BEN POPULATION <ul style="list-style-type: none">Mild Neutropenia is normal range for BEN population, continue treatmentObtain at least two baseline ANC levels before initiating treatmentIf treatment interrupted<ul style="list-style-type: none">< 30 days, continue monitoring as before≥ 30 days, monitor as if new patientDiscontinuation for reasons other than neutropenia	GENERAL POPULATION <ul style="list-style-type: none">Three times weekly until ANC ≥ 1500/μLOnce ANC ≥ 1500/μL, return to patient's last "Normal Range" ANC monitoring interval** BEN POPULATION <ul style="list-style-type: none">Weekly from initiation to 6 monthsEvery 2 weeks from 6 to 12 monthsMonthly after 12 months <ul style="list-style-type: none">See Section 2.4 of the full Prescribing Information
Moderate Neutropenia (500 to 999/μL)*	GENERAL POPULATION <ul style="list-style-type: none">Recommend hematology consultationInterrupt treatment for suspected clozapine induced neutropeniaResume treatment once ANC normalizes to ≥ 1000/μL BEN POPULATION <ul style="list-style-type: none">Recommend hematology consultationContinue treatment	GENERAL POPULATION <ul style="list-style-type: none">Daily until ANC ≥ 1000/μL, thenThree times weekly until ANC ≥ 1500/μLOnce ANC ≥ 1500/μL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval** BEN POPULATION <ul style="list-style-type: none">Three times weekly until ANC ≥ 1000/μL or ≥ patient's known baseline.Once ANC ≥ 1000/μL or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
Severe Neutropenia (less than 500/μL)*	GENERAL POPULATION <ul style="list-style-type: none">Recommend hematology consultationInterrupt treatment for suspected clozapine induced neutropeniaDo not rechallenge unless prescriber determines benefits outweigh risks BEN POPULATION <ul style="list-style-type: none">Recommend hematology consultationInterrupt treatment for suspected clozapine induced neutropeniaDo not rechallenge unless prescriber determines benefits outweigh risks	GENERAL POPULATION <ul style="list-style-type: none">Daily until ANC ≥ 1000/μLThree times weekly until ANC ≥ 1500/μLIf patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/μL BEN POPULATION <ul style="list-style-type: none">Daily until ANC ≥ 500/μLThree times weekly until ANC ≥ patient's established baselineIf patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1000/μL or at patient's baseline

* Confirm all **initial** reports of ANC less than 1500/μL (ANC < 1000/μL for BEN patients) with a repeat ANC measurement within 24 hours

** If clinically appropriate

The Covid-19 Caveat

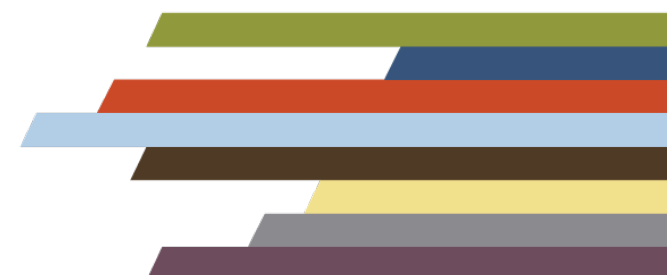
- On March 22, 2020, the FDA offered guidance allowing patients to receive [clozapine](#) in the absence of laboratory testing of ANC if there are compelling reasons not to complete the testing.
- It may be reasonable to forego testing in patients who have received the drug for at least one year because the risk of severe neutropenia is very low.
- If symptoms such as sore throat and fever develop during a period without ANC monitoring one should obtain an ANC and be assessed for clozapine-associated neutropenia.

<https://www.uptodate.com/contents/guidelines-for-prescribing-clozapine-in-schizophrenia#H692269627>



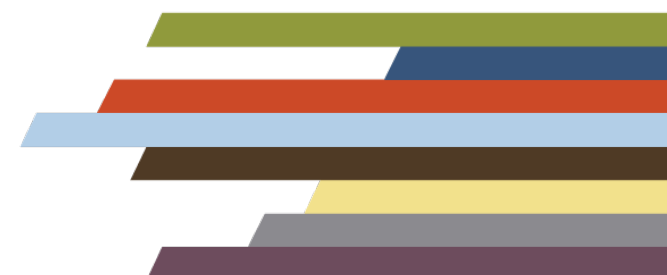
Clozapine Dosing

- Start at a low dose (12.5 to 25 mg/day). Initially twice or three times daily dosing to minimize autonomic side effects, like orthostatic hypotension, and sedating effects.
- Dose can be increased gradually, typically by 12.5 to 25 mg every one to two days, with the target dose and frequency determined by the plasma clozapine level and adverse effects.
- A clozapine plasma level can be checked after an initial target dose is reached, typically in about 2 weeks.
 - A [clozapine](#) plasma level in the range of 250 to 350 ng/mL is a reasonable target.
- Orthostatic blood pressure should be monitored daily when feasible (ie, in inpatient setting).



Clozapine Discussion

1. Indications: some people think Clozapine is the best mood stabilizer for refractory bipolar
2. Pretreatment assessment: EKG only necessary in elderly, cardiac disease, and other antipsychotics at high doses with QTC elongation (Seroquel)
3. Clozapine monitoring: Benign ethnic neutropenia (BEN)
 - Increased monitoring only when ANC less than 1000
 - If ANC >500:3 times weekly until >ANC 1000
4. What to do if ANC drifting down yet >1000
 - Lithium low dose 300 mg
5. Pros and cons of dosing Clozapine all at night
 - 2 week titration to 300 mg by increasing 25 mg QHS
 - Usual oral dose range 300-500 mg initially
 - Connection between oral dose and levels



Clozapine Discussion

6. When to check Clozapine levels:
 - Side effects > expected
 - Side effects < expected
 - No response at usual therapeutic dose
7. Oral Clozapine interruption >48 hours
 - Must “stop” and restart Clozapine at 25 mg and titrating again
8. Clozapine and rebound psychosis
9. Luvox/fluvoxamine: substantial increased blood levels
 - Case example
10. Clozapine plus ECT
 - Case report
11. Strategies to mitigate weight gain and metabolic syndrome

