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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

CLOZAPINE

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OCTOBER 2021

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

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OUTLINE

- Background
- Efficacy
- When to Use
  - Treatment resistant, treatment failures, structural and social supports
- Navigating the REMS
  - Roles for provider, designee, pharmacy
- Monitoring and managing adverse effects
- Odds and Ends
  - Starting/Stopping
  - Drug-Drug Interactions
  - Help

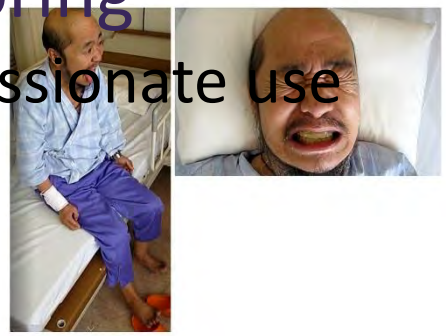
THE BACK STORY

- Early 1950s- Chlorpromazine discovered in Paris
  - "Neuroleptic dogma"- Expectation that "typical" APs produce EPS
- Late 1950s-Clozapine discovered in Berne, Switzerland
  - Dubbed "atypical" Lacked motor side effects and catalepsy in animal models
  - Hypothesized to be ineffective

Meltzer 2012

THE BACK STORY

- 1972-1975-approved for use in several European countries
- 1975-Finland-cluster of geriatric deaths r/t agranulocytosis
  - Withdrawal from European markets, cessation of research
- 1977-Sandoz proposes weekly monitoring
  - US study stopped, but open label compassionate use continued
- ***Effectiveness in tardive dyskinesia observed***



Meltzer 2012

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US CLOZAPINE TRIAL

- Early 1980s Sandoz rekindles research
- FDA required study in treatment resistant population
- Sandoz Clozapine Trial #30
  - 16 sites across US, 268 pts randomized in double blind fashion
  - Failed to respond to 3 prior AP trials at dosages ≥ chlorpromazine 1000mg/d
  - Failed to respond to Haldol (up to 60mg/d) x 6 weeks
  - Titrated to clozapine 500mg/d or chlorpromazine 1000mg/d in 2 weeks!
  - Weekly monitoring (CBC, EPS)
  - Chlorpromazine response plateaued by Week 3
  - Clozapine response continued to increase even past Week 6
  - Improved negative sx!

Meltzer 2012 Kane 1988

THE BACK STORY

- 1988- Publication of 2 landmark studies
  - Clear superiority over chlorpromazine
- FDA approved 1989 as a package (CPMS)
  - Sandoz partnered with Caremark (distribution) and Roche (lab)
  - Included med delivery, lab monitoring, lab reporting to provider
  - Price shocking and controversial ($8900/year)
  - State by state inclusion or exclusion by Medicaid systems
  - Led to lawsuits
    - States against Sandoz (antitrust)
    - Pt groups against states

Meltzer 2012

CLEAR SUPERIORITY

Table 6.—No. of Patients Whose Condition Improved*

Drug	No. (%) of Patients Whose Condition Improved	All Others, No. (%)	Total, No. (%)
Clozapine	38 (30)	88 (70)	**126 (100)**
Chlorpromazine	5 (4)	136 (96)	**141 (100)**
Total	**43** (16)	**224** (84)	**267 (100)**

*The categorization is based on the last evaluation completed for each patient. $P<.001$ by two-tailed Fisher's exact test.

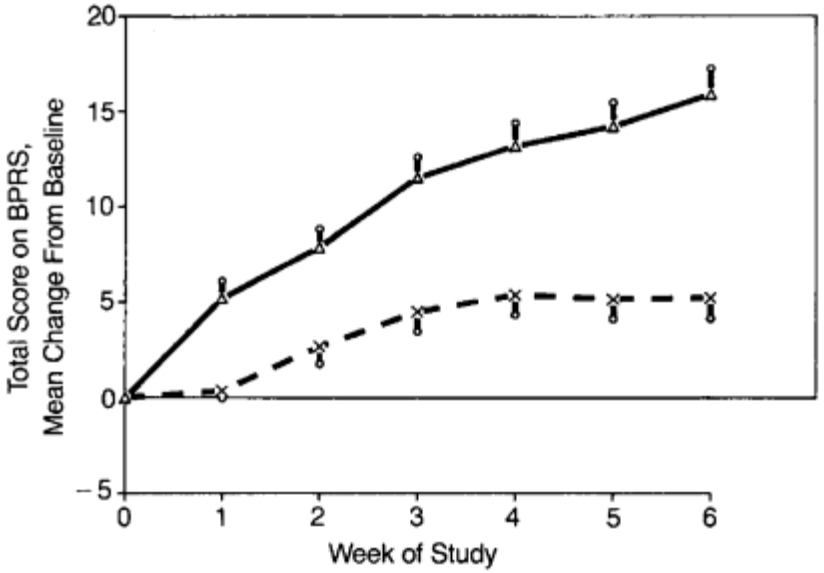
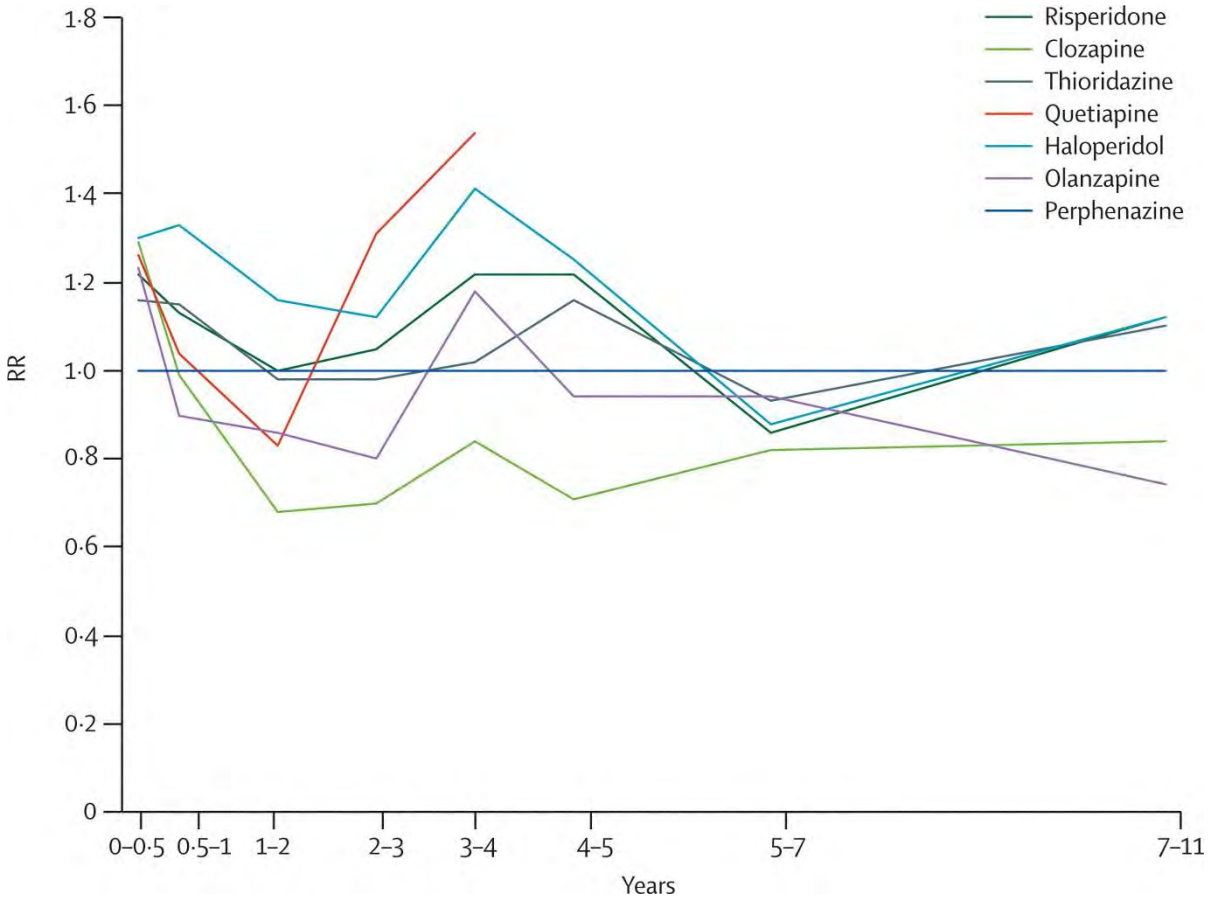


Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P<.001$ during each week of study.

Kane 1988



Tiihonen 2009

Mortality Impact

- Analysis over 11y in pts with schizophrenia v general pop

- Long term exposure to ***any*** AP lowers mortality
- Perphenazine as reference of 1.0
- Clozapine lowest mortality
  - (0.74, 0.6-0.91; p=0.0045
- Quetiapine highest mortality 1.45, CI1.09-1.82)

- **26% reduction in mortality with use of clozapine**

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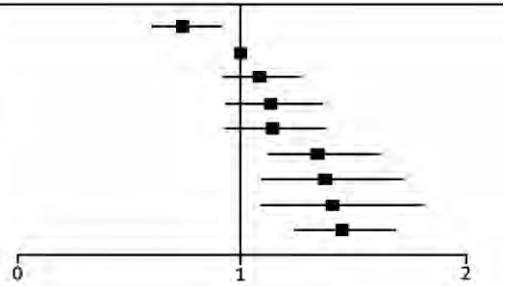
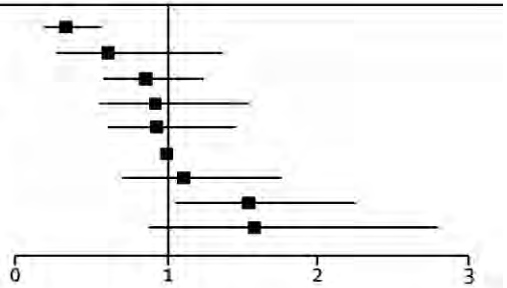
A Mortality by Any Cause

	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	182	32000	5·69	0·53 (0·43–0·65)	0·74 (0·60–0·91)
Perphenazine	193	17930	10·77	1·00	1·00
Polypharmacy	1481	132320	11·19	1·04 (0·89–1·21)	1·08 (0·92–1·26)
Olanzapine	264	25130	10·50	0·98 (0·81–1·17)	1·13 (0·93–1·36)
Thioridazine	227	18420	12·32	1·14 (0·94–1·39)	1·14 (0·93–1·38)
Risperidone	295	19410	15·20	1·41 (1·18–1·69)	1·34 (1·12–1·62)
Haloperidol	135	7040	19·19	1·78 (1·43–2·22)	1·37 (1·10–1·72)
Quetiapine	89	5360	16·60	1·54 (1·20–1·98)	1·41 (1·09–1·82)
Other	1234	70520	17·50	1·63 (1·40–1·89)	1·45 (1·24–1·69)



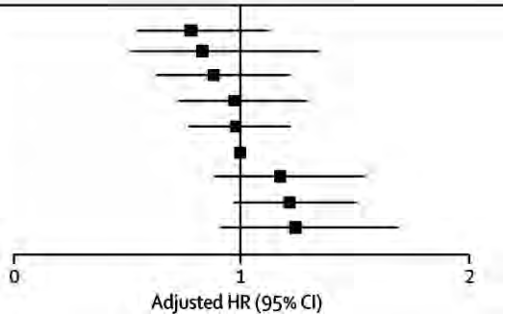
B Mortality by Suicide

Clozapine	27	32000	0·84	0·46 (0·28–0·76)	0·34 (0·20–0·57)
Haloperidol	7	7040	1·00	0·54 (0·24–1·22)	0·61 (0·27–1·37)
Polypharmacy	226	132320	1·71	0·93 (0·64–1·34)	0·86 (0·59–1·24)
Thioridazine	27	18420	1·47	0·80 (0·48–1·32)	0·93 (0·56–1·55)
Olanzapine	57	25130	2·27	1·23 (0·80–1·89)	0·94 (0·61–1·45)
Perphenazine	33	17930	1·84	1·00	1·00
Risperidone	47	19410	2·42	1·32 (0·84–2·05)	1·12 (0·72–1·76)
Other	194	70520	2·75	1·49 (1·03–2·16)	1·55 (1·07–2·25)
Quetiapine	19	5360	3·54	1·93 (1·09–3·39)	1·58 (0·89–2·79)



C Mortality by Suicide-Ischemic Heart Disease

Clozapine	42	32000	1·31	0·25 (0·17–0·35)	0·78 (0·54–1·12)
Quetiapine	21	5360	3·92	0·73 (0·46–1·17)	0·83 (0·52–1·34)
Olanzapine	65	25130	2·59	0·48 (0·35–0·66)	0·88 (0·63–1·21)
Thioridazine	104	18420	5·65	1·05 (0·80–1·39)	0·97 (0·73–1·29)
Polypharmacy	522	132320	3·94	0·74 (0·59–0·92)	0·97 (0·77–1·21)
Perphenazine	96	17930	5·35	1·00	1·00
Risperidone	119	19410	6·13	1·15 (0·88–1·50)	1·17 (0·89–1·54)
Other	520	70520	7·37	1·38 (1·11–1·71)	1·21 (0·97–1·51)
Haloperidol	72	7040	10·23	1·91 (1·41–2·59)	1·24 (0·91–1·69)



Tiihonen 2009

-Authors argue that Benefit outweighs adverse metabolic impact

-Authors pose that clozapine should be first line

GUIDELINES

Date	Source	Recommendation: clozapine to be prescribed or offered to patients		
		After failure of 2 adequate trials of 2 different AAs	With suicidal thoughts or behaviours	With persistent hostility and violent behaviours
2004	APA (US) [13]	X		
2005	CPA (CAN) [14]	X		
2007	TMAP (US) [15]	X (SGAs considered first-line)		
2009	NICE (UK) [16]	X (at least one of the drugs should be a non-clozapine SGA)		
2010	Schizophrenia PORT (US) [17]	X	X	X
2010	CADTH [18]	X		
2011	BAP (UK) [19]	X		X
2013	PAP (US) [20]	X (SGA, risperidone and olanzapine considered first-line)	X	X

Note: AA = antipsychotic agent, APA = American Psychiatric Association, BAP = British Association for Psychopharmacology, CADTH = Canadian Agency for Drugs and Technology in Health, CPA = Canadian Psychiatry Association, PAP = Psychopharmacology Algorithm Project, PORT = Patient Outcomes Research Team, TMPA = Texas Medication Algorithm Project.

Warnez 2014

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WHEN TO USE

- **Failure to respond to 2 previous ant trials**
  - Adequate dose, duration
    - **Usual doses for 4-6 weeks *OR* Max tolerated dose for 4-6 weeks**
  - Usually from 2 separate classes (typical, atypical)

- Treatment Resistant Schizophrenia
  - About 30% of all pts with schizophrenia
  - Estimated 10% of first episode pts within 1 year
  - Estimated 20% after years of previously responding to other APs

Meltzer 2012

WHEN TO USE…

- Lit Support for the following scenarios
  - High Risk for Suicide
  - Reduction in Mortality
  - Relapse requiring Rehospitalization
  - Improvement in cognition
- Also used:
  - Tx Resistant Bipolar disorder
  - Parkinson's Disease
  - Young pts with tx refractory schizophrenia (NICE)
  - Persistent positive sx (PORT)

WHEN TO USE…

- Support for
  - Help with Med Management, Med Monitoring?
  - Transportation to Lab/Pharmacy?
    - Disorganization
    - Paranoia
    - $$$$
    - Distance

- MSW?
- Peer Bridger?
- Case Manager?
- Pharmacy in clinic?

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CLINICIANS SURVEYED CITED THE BIGGEST BARRIER TO CLOZAPINE USE AS….

- A. Agranulocytosis Risk
- B. Registration Process with REMS
- C. Unfamiliarity with Drug
- D. Pt refusing blood draws

Kelly 2018

UNDERUTILIZED IN US

- Australia-35%
- China- 30%
- Enlgand-22%
- Sweden-20%
- Germany-20%

Love 2016

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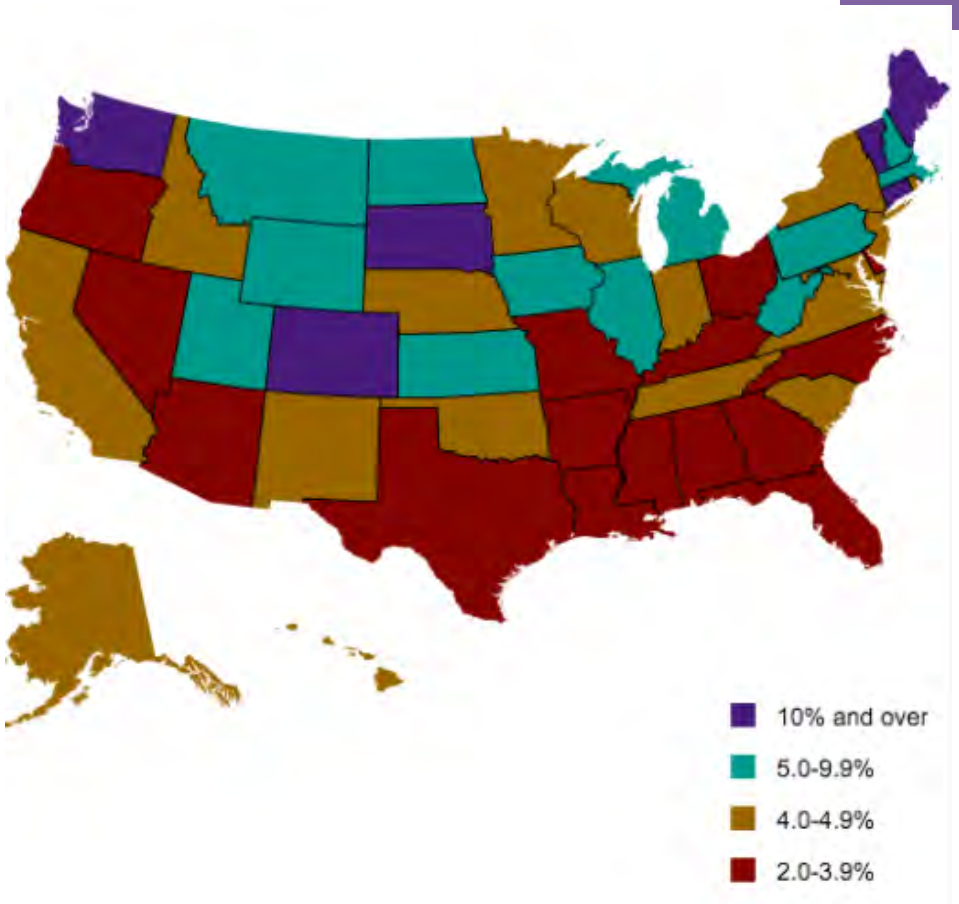
CLOZAPINE USE BY STATE

- Report from the National Association of State Mental Health Program Directors (2016)
- Continuously shrinking market share
  - 1999-11% nationally
  - 2008- 4% nationally
  - Now?



Love 2016

REMS MONITORING

- Just Kidding
  - ~~clozapinerems.com~~
- Old Website

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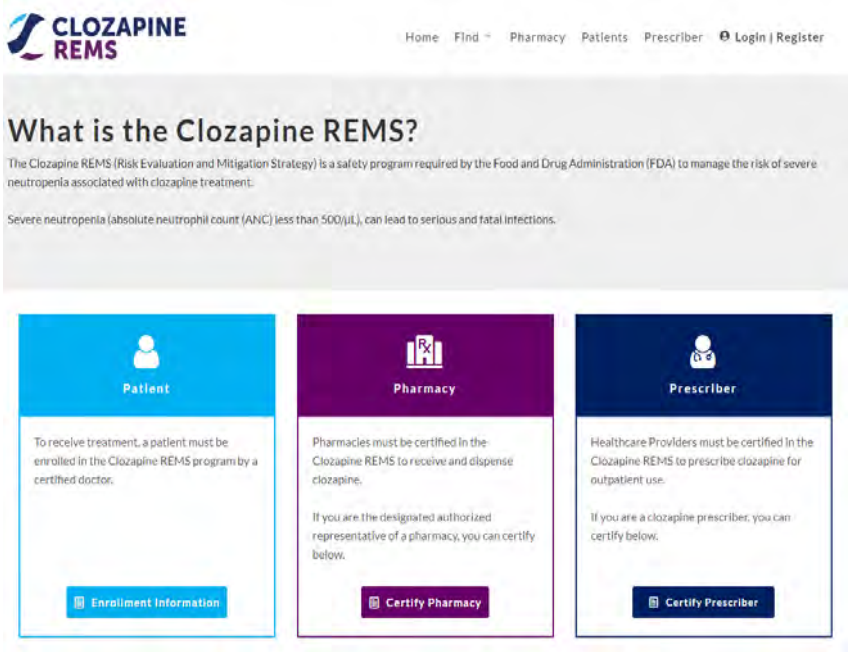
REMS MONITORING



- New Clozapine REMS
  - newclozapinerems.com
- New website and New REMS begins 11/15/21
  - May be delayed
- Why?
  - New vendor chosen by clozapine manufacturers
  - “Reduce health professional burden”

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REMS MONITORING: NO BLOOD, NO DRUG

- Intent is to ensure clozapine is dispensed only after ensuring a pt's labs are WNL and up to date
- Patient, Prescriber, Pharmacy must be enrolled (or re-enrolled)
- Historical archived patient data useful
  - ID your Jane Doe, prior dosing, prior lab trends, DNR lists

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REMS MONITORING: CHANGES AND CONCERNS

- Can provide data to REMS via paper or website
- Monthly submission of Patient Status Forms required versus weekly reporting
- Prescriber designates monitoring frequency versus REMS site (?)
- No carryover of historical patient data
- No carryover of *National Non-Rechallenge Master File* (NNRMF) or the *Do Not Rechallenge List*
- No requirement to report actual lab values
  - Select a box reflecting categorization

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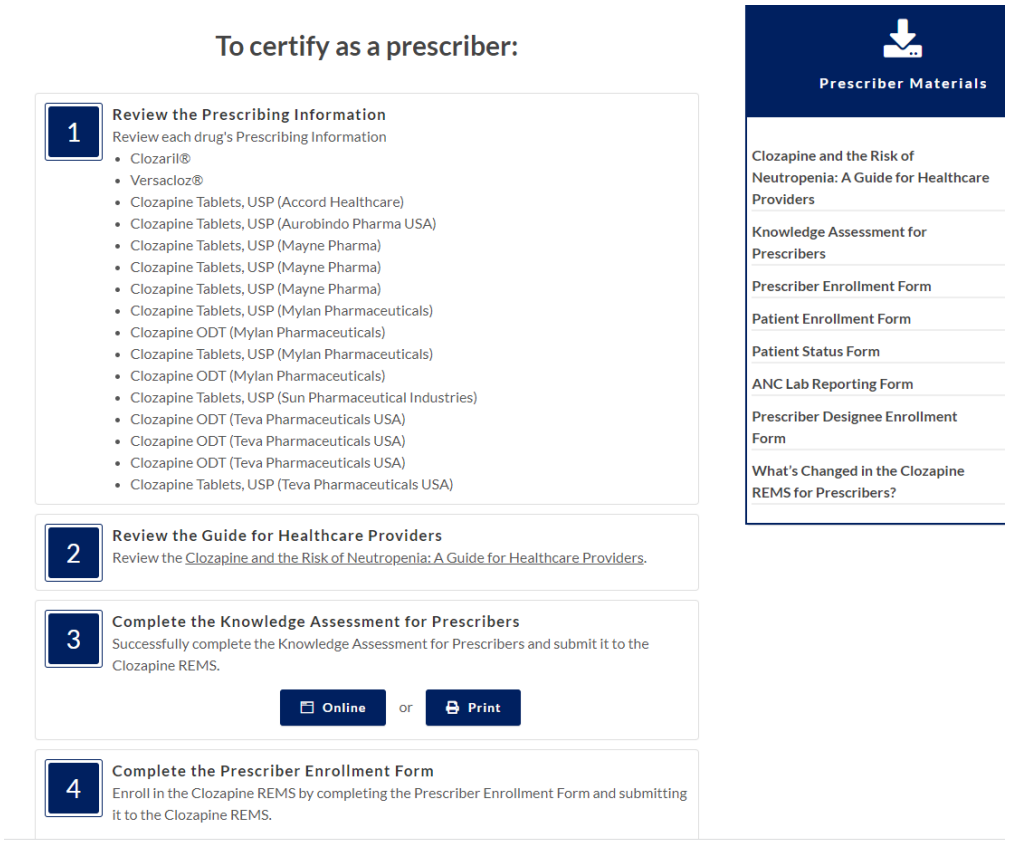
PRESCRIBER ENROLLMENT

- Create an account with NPI (or DEA?), ONE email account
- Pop quiz about acceptable baseline ANC, ANC monitoring



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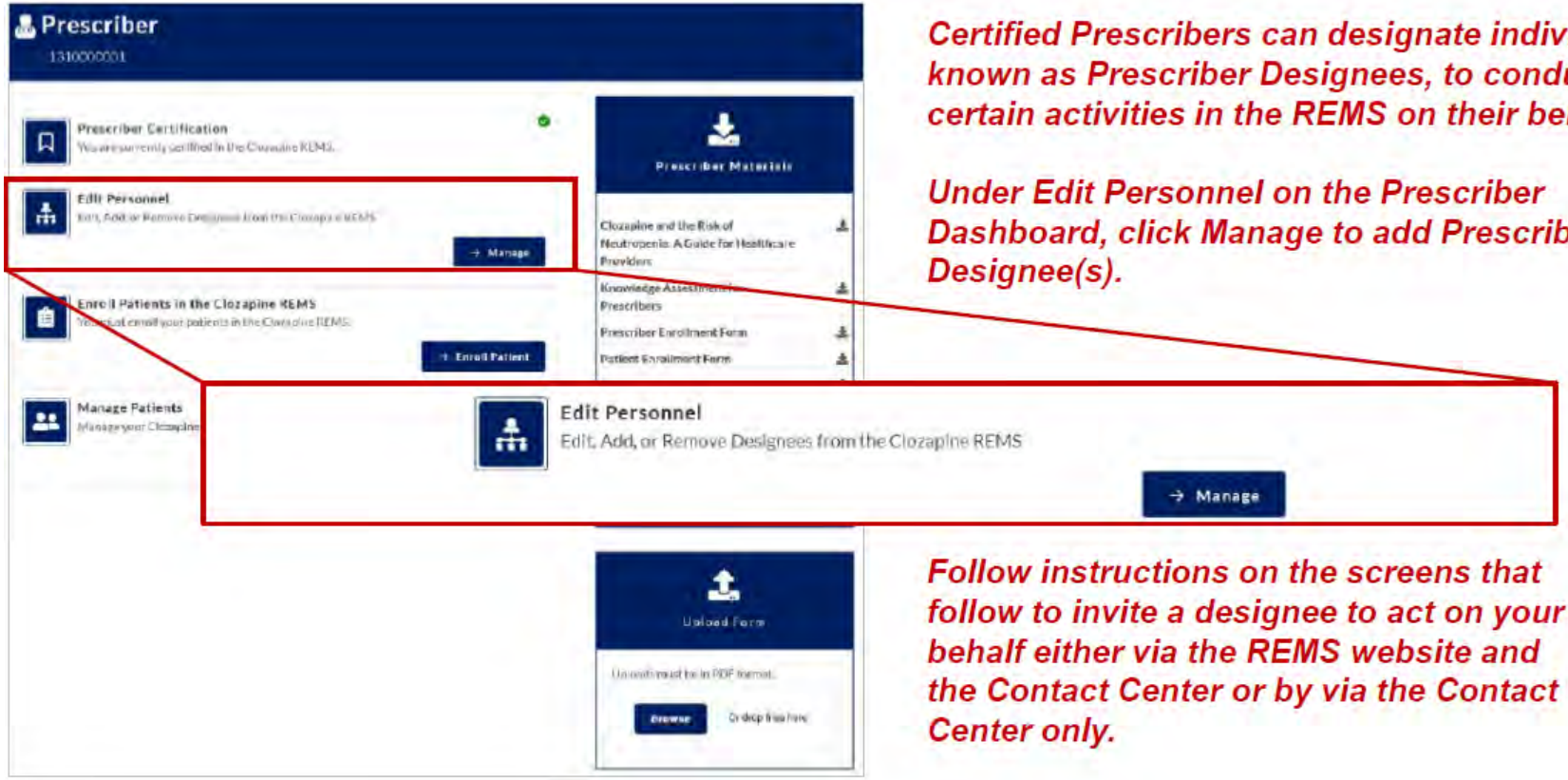
ADD A PRESCRIBER DESIGNEE



Certified Prescribers can designate individuals, known as Prescriber Designees, to conduct certain activities in the REMS on their behalf.

Under Edit Personnel on the Prescriber Dashboard, click Manage to add Prescriber Designee(s).

Follow instructions on the screens that follow to invite a designee to act on your behalf either via the REMS website and the Contact Center or by via the Contact Center only.

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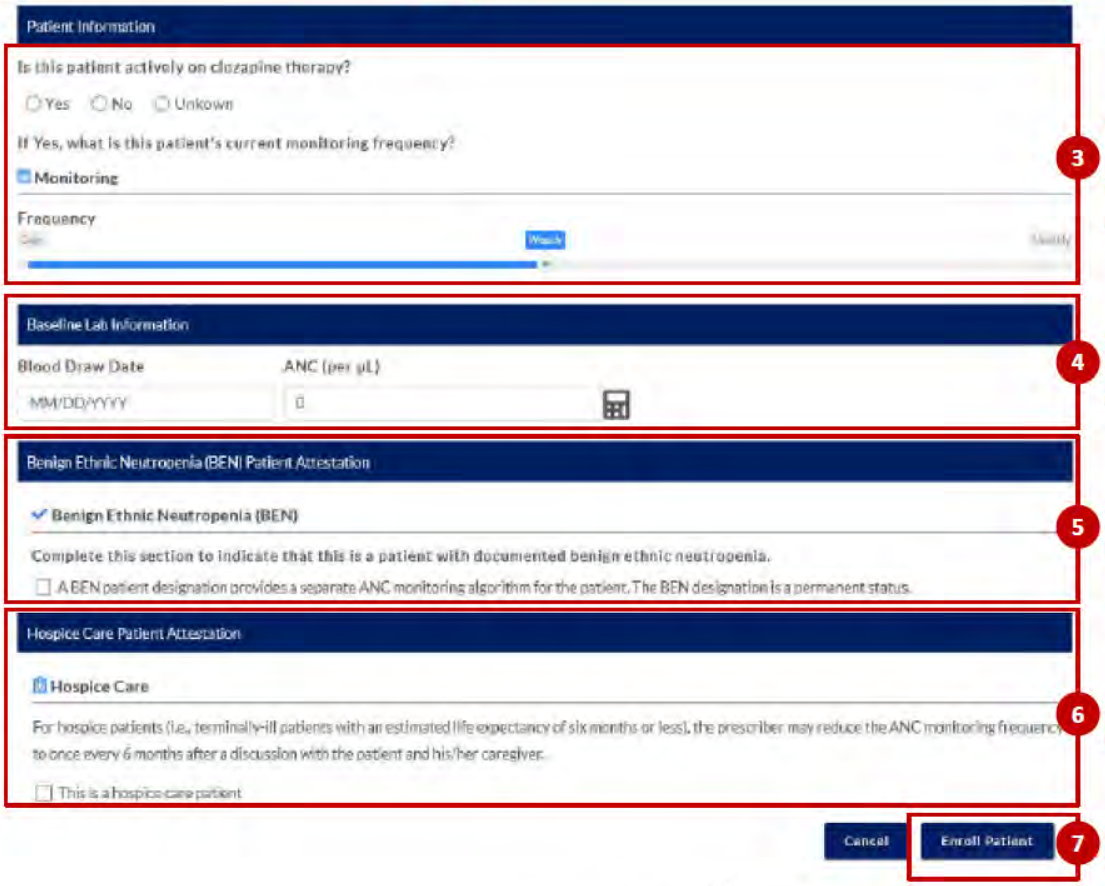
How to Enroll Patients (Continued)



3 ***...information about clozapine therapy (e.g., therapy status, monitoring frequency),...***

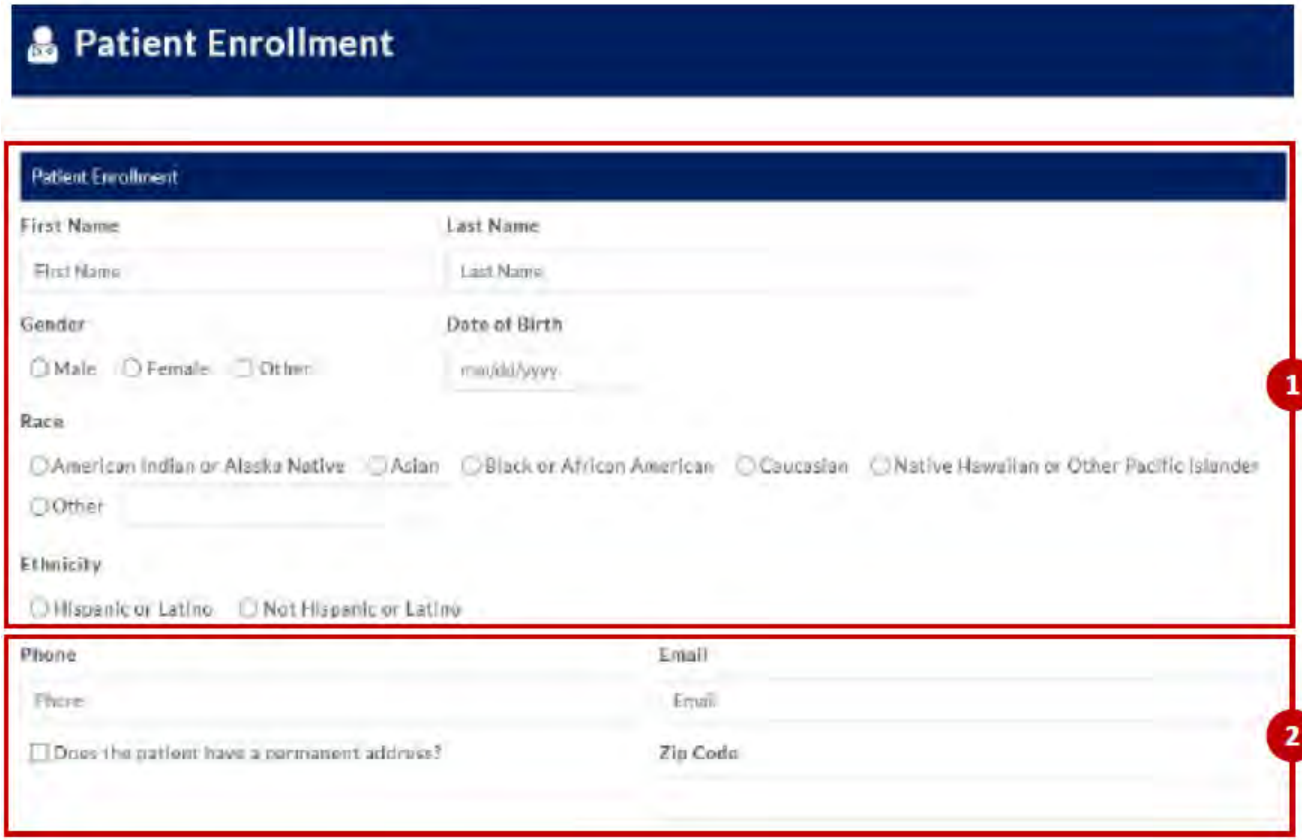
4 ***...baseline lab information (e.g., draw date, ANC),...***

5 ***...BEN status (if applicable),...***

6 ***...and hospice status (if applicable).***

7 ***Then click Enroll Patient.***

CLOZAPINE REMS



1

The Prescriber completes the Patient Enrollment form online by filling in information about the patient (e.g., name, DOB, demographics),…

2

…contact information (e.g., phone, email),…

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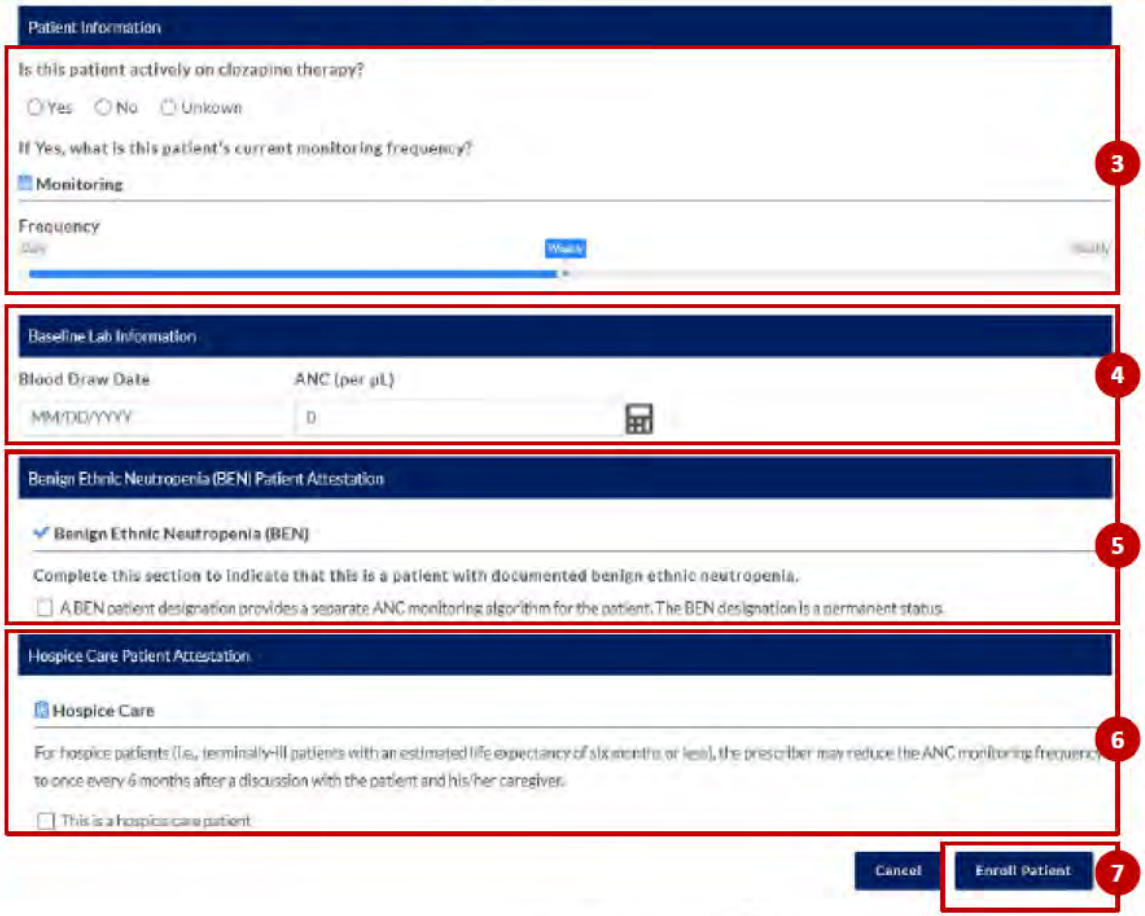
How to Enroll Patients (Continued)



3 ***...information about clozapine therapy (e.g., therapy status, monitoring frequency),...***

4 ***...baseline lab information (e.g., draw date, ANC),...***

5 ***...BEN status (if applicable),...***

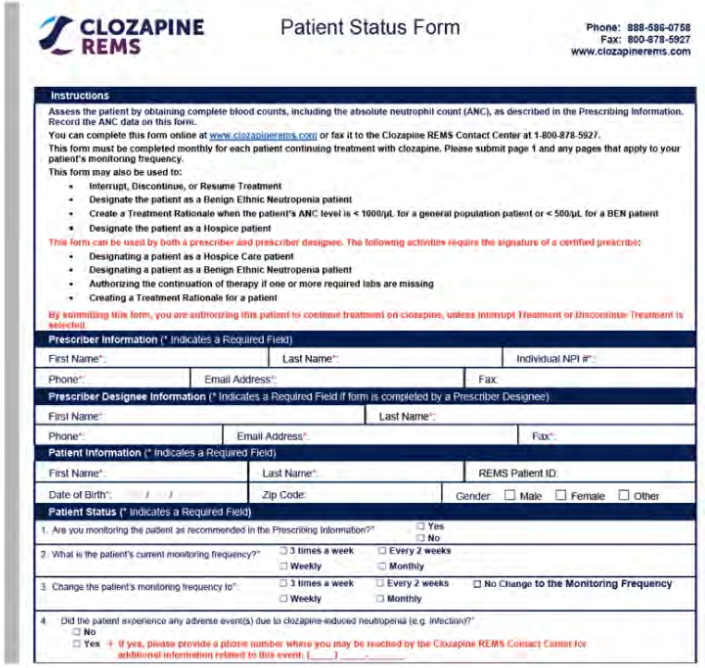
6 ***...and hospice status (if applicable).***

7 ***Then click Enroll Patient.***

CLOZAPINE REMS

PATIENT STATUS FORM

- Submission of monthly ANCs (or ranges)
  - Sections for monthly, every two week, weekly and three times per week monitoring frequencies
- Interrupt, discontinue or resume treatment
- Designate a patient as a Hospice Care Patient
- Designate a patient as a BEN patient
- Authorize continuation of therapy if labs are missing
- Record/change the monitoring frequency
- Create a *Treatment Rationale*



CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions

Assess the patient by obtaining complete blood counts, including the absolute neutrophil count (ANC), as described in the Prescribing Information. Record the ANC data on this form.

You can complete this form online at www.clozapinerems.com or fax it to the Clozapine REMS Contact Center at 1-800-878-5927.

This form must be completed monthly for each patient continuing treatment with clozapine. Please submit page 1 and any pages that apply to your patient's monitoring frequency.

This form may also be used to:

- Interrupt, Discontinue, or Resume Treatment
- Designate the patient as a Benign Ethnic Neutropenia patient
- Create a Treatment Rationale when the patient's ANC level is < 1000/µL for a general population patient or < 500/µL for a BEN patient
- Designate the patient as a Hospice patient

This form can be used by both a prescriber and prescriber designee. The following activities require the signature of a certified prescriber:

- Designating a patient as a Hospice Care patient
- Designating a patient as a Benign Ethnic Neutropenia patient
- Authorizing the continuation of therapy if one or more required labs are missing
- Creating a Treatment Rationale for a patient

By submitting this form, you are authorizing this patient to continue treatment on clozapine, unless Interrupt Treatment or Discontinue Treatment is selected.

Prescriber Information (* Indicates a Required Field)

First Name*: | Last Name*: | Individual NPI #*:

Phone*: | Email Address*: | Fax:

Prescriber Designee Information (* Indicates a Required Field if form is completed by a Prescriber Designee)

First Name*: | Last Name*:

Phone*: | Email Address*: | Fax*:

Patient Information (* Indicates a Required Field)

First Name*: | Last Name*: | REMS Patient ID:

Date of Birth*: / / | Zip Code: | Gender: ☐ Male ☐ Female ☐ Other

Patient Status (* Indicates a Required Field)

1. Are you monitoring the patient as recommended in the Prescribing Information?* ☐ Yes ☐ No

2. What is the patient's current monitoring frequency?* ☐ 3 times a week ☐ Every 2 weeks ☐ Weekly ☐ Monthly

3. Change the patient's monitoring frequency to*: ☐ 3 times a week ☐ Every 2 weeks ☐ No Change to the Monitoring Frequency ☐ Weekly ☐ Monthly

4. Did the patient experience any adverse event(s) due to clozapine-induced neutropenia (e.g. infection)?* ☐ No ☐ Yes → If yes, please provide a phone number where you may be reached by the Clozapine REMS Contact Center for additional information related to this event: (____) _____-_____

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PATIENT STATUS FORM

Weekly Monitoring Frequency (Enter data for the last four weekly blood draws for this patient)

Blood Draw Date	General Patient Population	BEN Patient Population		ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.

[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

PHARMACY RESPONSIBILITIES

- Must enroll in REMS to be able to purchase clozapine from wholesalers
- Must obtain a(n) *REMS Dispense Authorization* (RDA) to dispense rx
  - Only available from REMS website, call center
  - Ensures labs up to date, WNL, PSF sent in last 37d, prescriber has authorized tx if labs are missing or labs are below normal range
- Can submit ANCs via *ANC Lab Reporting Form*
- Can override system 3 times per year with a *Dispense Rationale*
- Can reverse an RDA (so pt can fill elsewhere) (?)

SUMMARIZING LOGISTICS OF INITIATION

- Enroll as provider
- Enroll patient*
- Assign prescriber designee to help with ANC reporting, pt enrollment
- Find a clozapine friendly pharmacy (also enrolled)*
- Find a lab and Draw Baseline ANC*
- Report ANCs to REMS*
- Prescribe Clozapine in appropriate increments (7d, 14d, 28d)

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POP QUIZ: WHICH OF THE FOLLOWING IS TRUE?

- QTc prolongation is the most common adverse effect associated with clozapine.
- Risk for clozapine associated myocarditis is higher with higher doses.
- Neutropenia risk decreases after 6 months of clozapine use.
- Neutropenia risk increases with higher doses of clozapine.

MONITORING AND MANAGING ADVERSE EFFECTS

- Dose Dependent
  - Sedation
  - Anticholinergic
    - Constipation
  - Orthostasis
  - Seizure

- Independent of Dose
  - Neutropenia
  - Granulocytopenia
  - Myocarditis
  - Metabolic Changes
  - Drooling?

ADVERSE EFFECTS

Common Adverse Reactions (≥5%) in the 6-Week, Randomized, Chlorpromazine-controlled Trial in Treatment-Resistant Schizophrenia

Adverse Reaction	CLOZARIL (N=126) (%)	Chlorpromazine (N=142) (%)
Sedation	21	13
Tachycardia	17	11
Constipation	16	12
Dizziness	14	16
Hypotension	13	38
Fever (hyperthermia)	13	4
Hypersalivation	13	1
Hypertension	12	5
Headache	10	10
Nausea/vomiting	10	12
Dry mouth	5	20

Clozapine Prescribing Info 2020

ADVERSE EFFECTS

Adverse Reactions	CLOZARIL N=479 % Reporting	Olanzapine N=477 % Reporting
Salivary hypersecretion	48	6
Somnolence	46	25
Weight increased	31	56
Dizziness (excluding vertigo)	27	12
Constipation	25	10
Insomnia	20	33
Nausea	17	10
Vomiting	17	9
Dyspepsia	14	8

Clozapine Prescribing Info 2020

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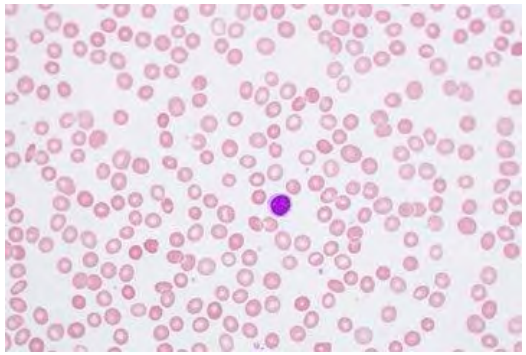
NEUTROPENIA AND AGRANULOCYTOSIS

- Mild neutropenia
  - ANC 1,000-1,499/mm^3
- Moderate Neutropenia
  - ANC 500-999/mm^3
- Severe Neutropenia
  - ANC<500/mm^3

- Risk Factors?
  - Ashkenazi Jewish descent
  - Elderly
  - HLA-B38, DR4 DQw3 allelic variants
  - CYP metabolizing differences?
  - Concomitant ABX?
  - Infection?
  - ?

NEUTROPENIA AND AGRANULOCYTOSIS



- 0.7-2.0%
- Dose independent, idiosyncratic
  - Toxic metabolite?
  - Bone marrow immunologic processes
- 2 Subtypes Hypothesized
  - Mild to Moderate (500-1500) with recovery 2-8d (1.8%)
  - Severe (<500) (0.78%)
    - Even when stopped at ANC ~1000, progresses to severe in 2-5d
    - Lasts 14-21d
- Highest risk during first 6-18 weeks of tx

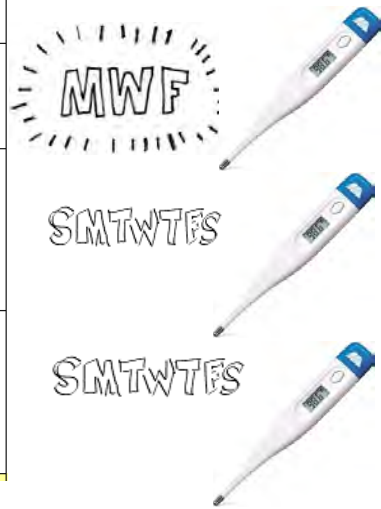
Meltzer, Raja, Nielsen

NEUTROPENIA AND AGRANULOCYTOSIS

CLOZAPINE TREATMENT RECOMMENDATIONS BASED ON ABSOLUTE NEUTROPHIL COUNT (ANC) MONITORING		
ANC LEVEL	**TREATMENT RECOMMENDATION**	**ANC MONITORING**
GENERAL POPULATION		

NORMAL (≥ 1500/µl)	• Initiate treatment.
	• If treatment interrupted:
	  • < 30 days, continue monitoring as before.
	  • ≥ 30 days, monitor as if new patient.
		• Weekly from initiation to 6 months.
		• Every 2 weeks from 6 to 12 months.
		• Monthly after 12 months.

MILD NEUTROPENIA (1000-1499/µl)*	• Continue treatment.	• Three times weekly until ANC ≥ 1500/µl. • Once ANC ≥ 1500/µl, return to patient's last "Normal Range" ANC monitoring interval.**
MODERATE NEUTROPENIA (500-999/µl)*	• Recommend hematology consultation. • Interrupt treatment for suspected clozapine induced neutropenia. • Resume treatment once ANC normalizes to ≥ 1000/µl.	• Daily until ANC ≥ 1000/µl then, • Three times weekly until ANC ≥ 1500/µl. • Once ANC ≥ 1500/µl, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval.**
SEVERE NEUTROPENIA (< 500/µl)*	• Recommend hematology consultation. • Interrupt treatment for suspected clozapine induced neutropenia. • Do not rechallenge unless prescriber determines benefits outweigh risks.	• Daily until ANC ≥ 1000/µl then, • Three times weekly until ANC ≥ 1500/µl. • If patient is rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µl.



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MANAGEMENT OF NEUTROPENIA/AGRANULOCYTOSIS

- Risk of death r/t agranulocytosis= 1/10,000
- Reversible in the majority of cases
- Can use G-CSF for tx and neutrophil recovery
- Literature support for rechallenge
  - Use of lithium hx
  - Use of G-CSF PRN or 2x/wk-3x/wk
    - Successful in ~60% of pts
  - Unsuccessful rechallenges show that dyscrasias occur more quickly and are more severe and of longer duration than first hematologic insult

Meltzer, Raja, Nielsen, Manu

BEN-BENIGN ETHNIC NEUTROPENIA

- WBC and ANC normal values based upon Caucasian ranges
- Lower WBC and ANC observed in persons of African descent
  - Occurrence of ANC <1500 cells/mm^3 without increased infection
  - M>F
  - Occurs in some Middle Eastern ethnicities
  - Can start clozapine safely in ANC of 1000 cells/mm^3
- Consider hematology consult to determine dx

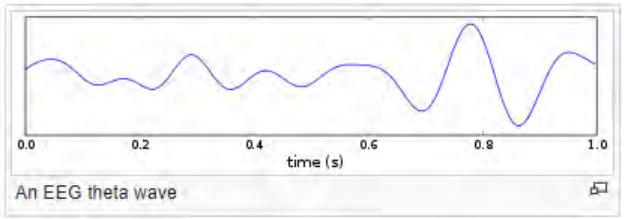
BEN AND HEALTH DISPARITIES

- Likely related to variants of DARC Gene
  - Duffy Antigen Receptor Chemokine
- Led to reduced initiation of clozapine in African Americans
  - 10.3% v 15.3% in MD study
- Led to an increase in d/c of clozapine for neutropenia
  - 5.3% v 2.4% over 10y
  - **Less likely to develop severe neutropenia** !
    - 0% v 0.62%

Kelly 2007

SEIZURE

- Dose Dependent lowering of seizure threshold
  - Can be related to rapid titrations
  - >600mg/d = 4.4%
  - 300-600mg/d= 2.7%
  - <300mg/d 1.0%
- 50-60% of pts display EEG abn[illegible]
- Seizure type
  - Presents as Generalized Tonic-Clonic, myoclonus can occur



Raja Nielsen

SEIZURE MANAGEMENT

- Management
  - Reduce the dose or slow the titration
  - Likely consider initiation of antiseizure medication
    - Divalproex, lamotrigine, gabapentin, topiramate
  - 78% pts can likely continue
- Prevention
  - Check for any hx of seizure
  - Use standard dose titration, use split dosing v once daily dosing
  - *Consider* monitoring clozapine levels
    - Upper lab limit of 1,000ng/ml is not well established
    - Case reports in levels >1,300ng/ml
    - Wide interpatient variability

Raja

MYOCARDITIS

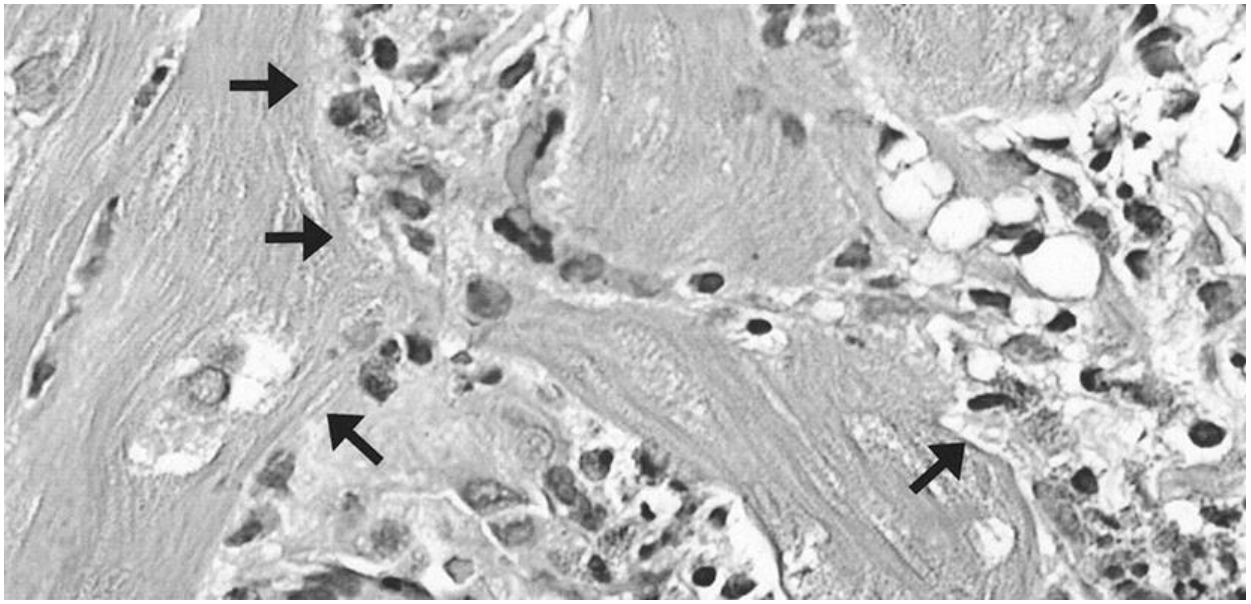


Image by Pieroni M et al. Chest 2004;126: 1703-1705.

MYOCARDITIS

- Risk is 0.015- 0.188% higher in those taking clozapine
- 1/10,000 to 1/1,000
- Timing
  - During first month-75% ESPECIALLY the THIRD WEEK
  - During first two months-85%

- Risk factors?
  - Young, male patients
- Mortality- as high as 50%

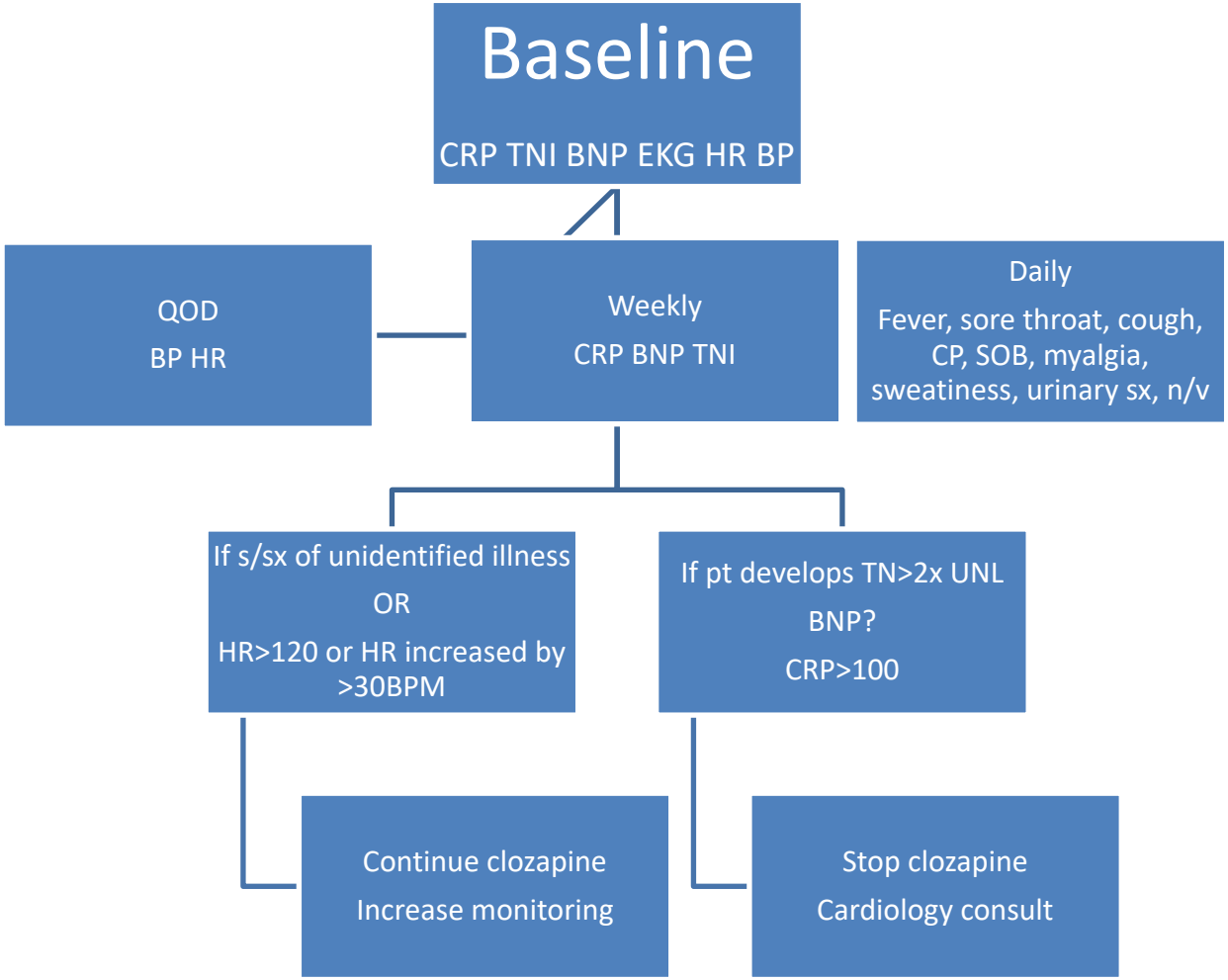
- Presentation
  - Nonspecific, difficult to detect
  - TEE and BNP monitoring?

Raja De Berardis

MYOCARDITIS

- Management
  - Early detection
  - D/C of clozapine
  - Tx with beta blocker, ACEI, diuretics; CCS uncertain benefit
  - Likely do not retrial
- Prevention
  - Monitor for tachycardia, CP, dyspnea, fever, flu like sx or eosinophilia
  - Weekly monitoring?
    - CKMB
    - CRP
    - Troponins
  - Low

AUSTRALIA AND NZ MONITORING



De Bernardis, Ronaldson

CONSTIPATION

- 16%- PI
- 33-60%-Lit
- 50%- Real HMC pts
- 66%+- Real HMC pts with scheduled bowel meds

- Possible (obstruction, prolonged postop ileus, nec colitis, peritonitis, bowel perf, *death)*

Raja

- Discuss baseline bowel care, motility
- Bowel Care usually scheduled with clozapine starts
- Bowel Care PRNs always added to clozapine starts
- Streamline anticholinergics within current med list

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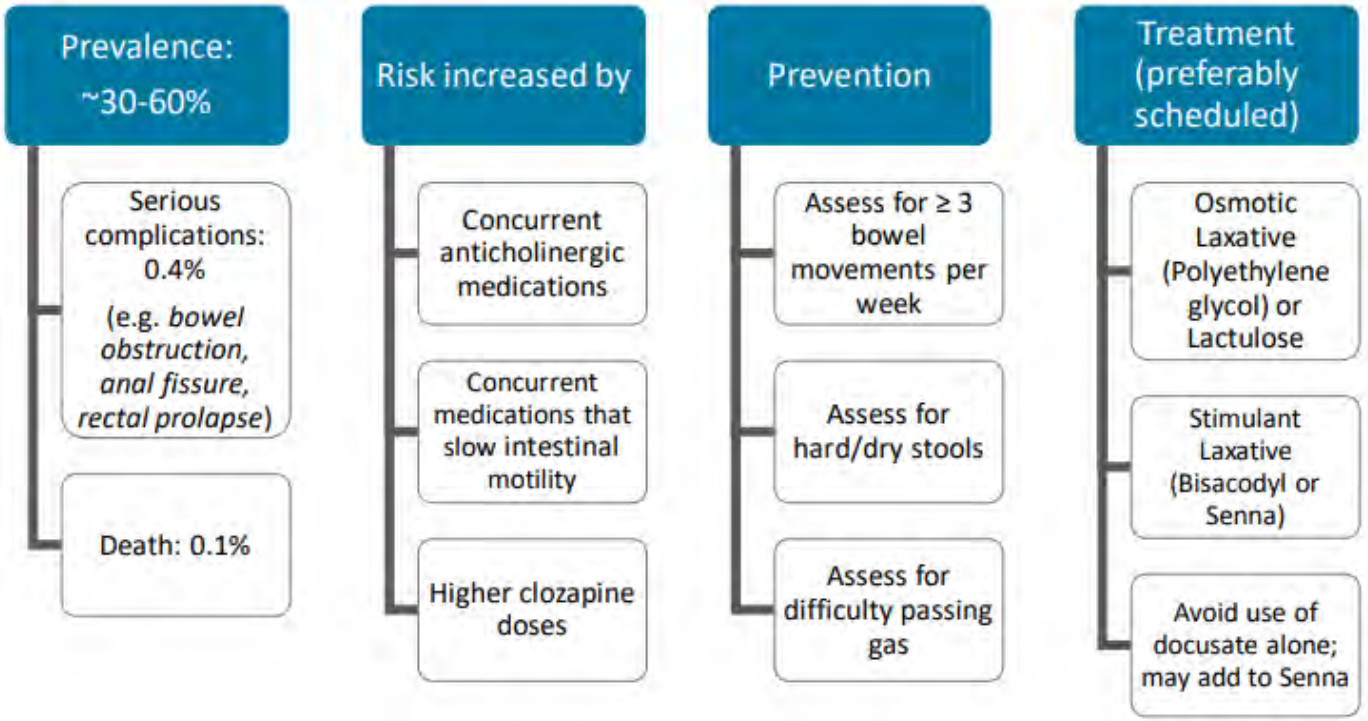
CLOZAPINE OVERVIEW



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CONSTIPATION

- Miralax
- Senna
- Bisacodyl PO or PR
- Lubiprostone

- Rescue:
- Beware bulk agents

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For all clozapine patients

- Discontinue other constipating medications (especially other anticholinergics), if possible (see page 11).
- Increase daily fluid and fiber intake (cereals, wheat bran, fruits and vegetables).
- Encourage regular exercise.

Minimal or mild symptoms of bowel slowing or constipation

- Change to an antipsychotic with less anticholinergic effects, if possible.
- Reduce antipsychotic dose, if possible.
- **Docusate** (softener/surfactant) 100 mg orally daily or twice daily, may have very minimal efficacy.
- **Polycarbophil** (fiber supplement/bulk forming agent) 2 tabs orally one to four times daily.
  - Dose must be increased slowly, effect will not be seen for several weeks.
  - Does not significantly increase stool transit time.

Moderate to severe symptoms of constipation

(or when bowel cleansing or "rescue" has been required):

- Change to an antipsychotic with less anticholinergic effects, if possible.
- Reduce antipsychotic dose, if possible.
- Osmotic agents recommended (first choice).
  - **lactulose**: 15-30 ml orally once or twice daily.
    Improves stool frequency and consistency, liquid formulation.
  - **polyethylene glycol powder** (PEG) (MiraLAX®) usual dose 17 gm (1 Tbsp), range 8.5 to 34 gm (1/2 to 2 Tbsp).
    Mixed in 8 oz fluid, taken orally once daily.
    Improves stool frequency and consistency, powder formulation.
- Stimulant laxatives (alternative or adjunct therapy with osmotic agents).
  - **bisacodyl** 5 mg tablets, 1-3 tablets orally once daily.
  - **bisacodyl** 10 mg suppositories, 1 suppository per rectum once daily.
  - **senna** 8.6 mg tablets, 1-2 tablets once or twice daily, may increase up to 10 tablets per day.
- Patients who are poorly responsive or unresponsive to maximal therapy with these agents alone or in combination should be referred for further management.

ORTHOSTASIS/TACHYCARDIA

- Streamline med list
- Use standard titration
- Split doses
- Check orthostatics during titration
- Can lead to syncope
- More pronounced with any antipsychotic except possibly IM chlorpromazine

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SIALORRHEA

- Incidence: 30-80%
- Counterintuitive
- Mechanism
  - M4 agonism
  - Alpha 2 agonism

- Treatment
  - Hx
  - Atropine ophthalmic drops 1%
  - Ipratropium
  - Glycopyrrolate

Raja

Treatment Option	Mechanism for Reduction of Saliva	Dosage Range	Notes
Anticholinergic Medications			
Benztropine Tablet	Muscarinic receptor antagonist	0.5-6mg daily	Increased risk of constipation
Atropine eye drops		1% place 1-6 drops sublingually daily	Needs multiple daily dosing Minimal systemic absorption Tell patient to swish drops around mouth if possible
Ipratropium Bromide Nasal Spray		0.03-0.06%, 2-6 sprays daily sublingually	Minimal systemic absorption Well tolerated Effect may not be long lasting, requiring multiple daily doses
Pirenzepine Tablet		25-100mg daily	Not available in the United States Side effects: Mild diarrhea may be common Does not cross blood-brain barrier
Trihexyphenidyl Tablet		2-15mg daily	Increased risk of constipation
Hyoscine (scopolamine)		0.4-0.8mg tablet daily 1.5mg patch every 72 hours	Patch was studied with greater improvement than that reported with oral treatment
Amitriptyline Tablet		25-100mg daily	Increased risk of constipation
Biperiden Tablet		6mg daily	Not available in the United States
Glycopyrrolate Tablet or Solution		1-8mg daily	Does not cross blood-brain barrier and may have less impact on cognitive functioning
Alpha$_2$-Adrenergic Antagonists			
Clonidine	Alpha$_2$-adrenergic receptor antagonist	0.05-0.1mg daily 0.1-0.2mg patch weekly	Postural hypotension may worsen in combination with clozapine Other side effects: Hypotension, sedation, dizziness, urinary retention, bradycardia, constipation
Terazosin Capsule		2mg at bedtime	
Guanfacine Tablet		1mg daily	
Other Treatments			
Sulpiride Tablet	Unknown, selectively binds D_2 and D_3 receptors	150-300mg daily	Not available in the United States May allow for decrease in clozapine dosage which can reduce hypersalivation
Amisulpride Tablet		400mg daily	
Botulinum Toxin	Inhibits acetylcholine release in salivary glands	150 international units injected into parotid glands	Side effects: pain, tenderness, bleeding RARE: jaw dislocation

NOTE: none of these treatment options are FDA approved for this indication and there are not established doses for this purpose

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TITRATION

- Usual starting dose is 25mg/d at HS, or 12.5mg HS for elderly
- Increase by 25mg/d with weighted doses at HS
- Target dose is usually 300-350mg/d initially, but dependent upon pt tolerability

- Provided in 25mg tablets, 100mg tablets usually
- Usually use 25mg tabs while titrating
  - Avoid half tabs…..
  - Think in terms of tabs per day

TITRATION SAMPLE FROM TEVA

EXAMPLE							
WEEK 1	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)	WEEK 2	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	12.5 (optional)	12.5–25	Day 8	75	100	175
Day 2	25	---	25	Day 9	100	100	200
Day 3	25	25	50	Day 10	100	125	225
Day 4	25	50	75	Day 11	100	150	250
Day 5	50	50	100	Day 12	125	150	275
Day 6	50	75	125	Day 13	150	150	300
Day 7	50	100	150	Day 14	150	150	300

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INTERRUPTIONS IN THERAPY

- Missed doses: cholinergic rebound
- Missed doses x 48h or greater:
  - Re-titrate and start with 25mg/d to avoid dose related ADEs: OHOTN, bradycardia, syncope
  - If tolerated, then may then titrate more quickly than initial dosing

- Missed doses 1d-30d
  - Resume current monitoring frequency (weekly, Q2W, Q4W) if ANC WNL
- Missed doses >30d
  - Restart at weekly ANC monitoring*

Clozapine Prescribing Info 2020

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DRUG INTERACTIONS

+

Up to 30% Lower Clozapine Levels!

2x-5x Higher Clozapine Levels!

Tsuda 2013

OTHERS TO CONTACT

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- CHAS Kellie Smith Jaime Fazzone

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