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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

CLOZAPINE

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JUNE 2025

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

WHAT'S NEW? WHAT'S OLD?

- Background and Efficacy
- When to Use
  - Guidelines
  - Structural and social supports

- Navigating REMS Changes
  - Prior roles for providers and pharmacies
  - New roles and practices
- Monitoring
  - Neutropenia and myocarditis
- Pharmacokinetics
  - Safe Titration
  - Therapeutic Drug Monitoring
  - Drug Interactions

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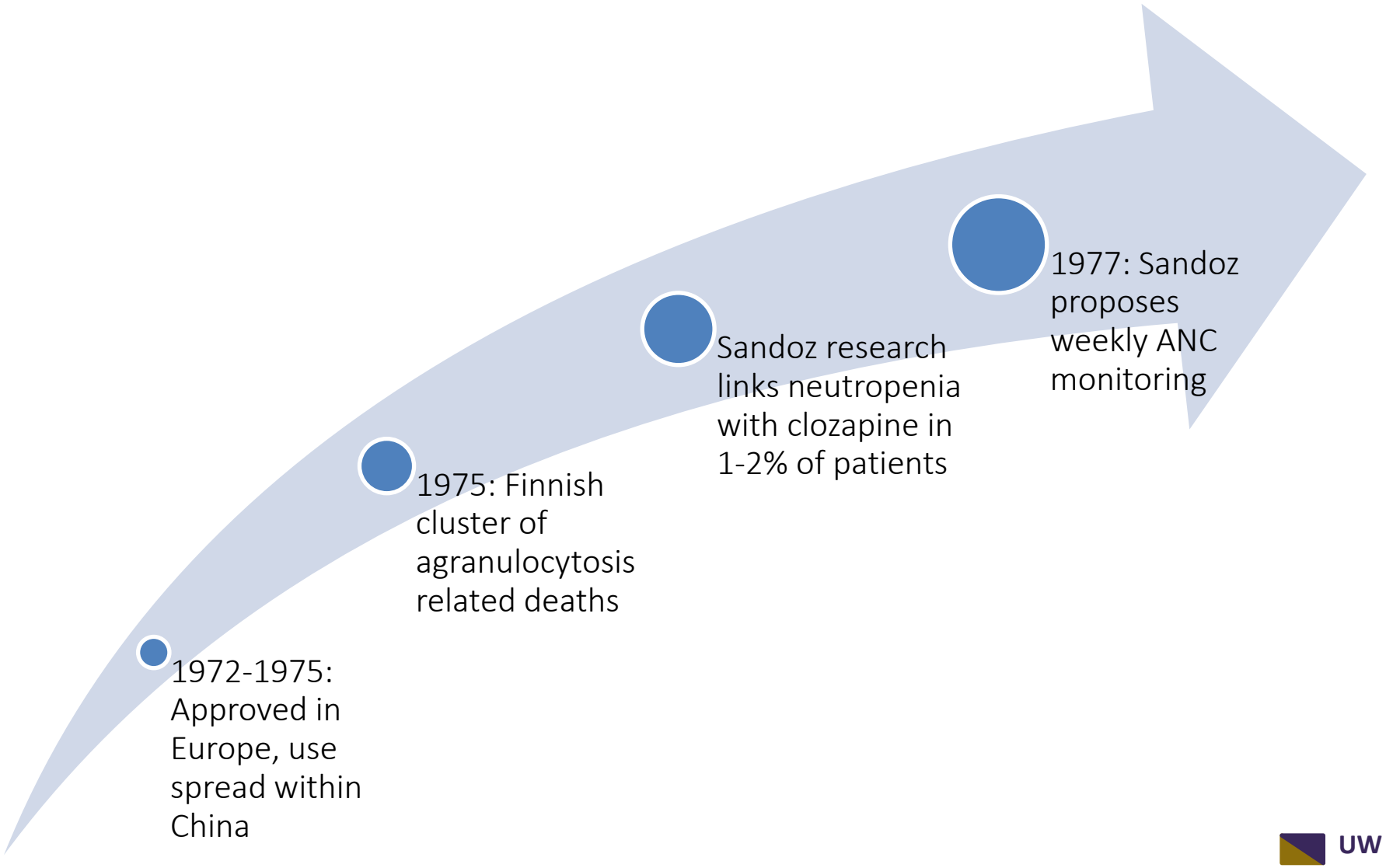
HISTORY OF NEUTROPENIA AND AGRANULOCYTOSIS



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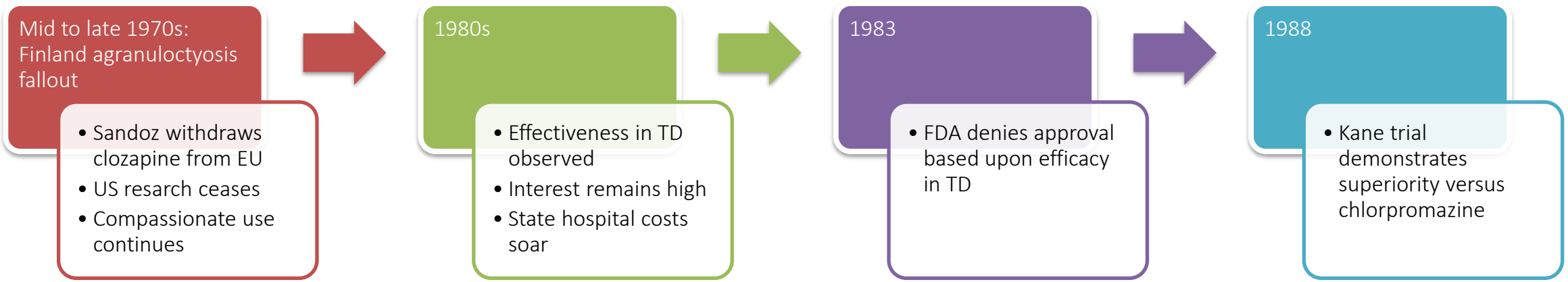
RESEARCH INTEREST REKINDLED



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KANE ET AL. A DEMONSTRATION OF CLOZAPINE'S EFFICACY

268 ***refractory*** patients randomized in double blind fashion x 6 weeks

- Refractory-Failed to respond to 3 prior AP trials at dosages ≥ Chlorpromazine 1000mg/day

Nonresponse to lead up period with failed response to Haldol (up to 60mg/day) x 6 weeks*

Titrated to clozapine 500mg/day or chlorpromazine 1000mg/day in 2 weeks*

Weekly monitoring (BPRS, CGI, CBC, EPS)

*Doses are larger than what is acceptable in current standards of practice

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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.

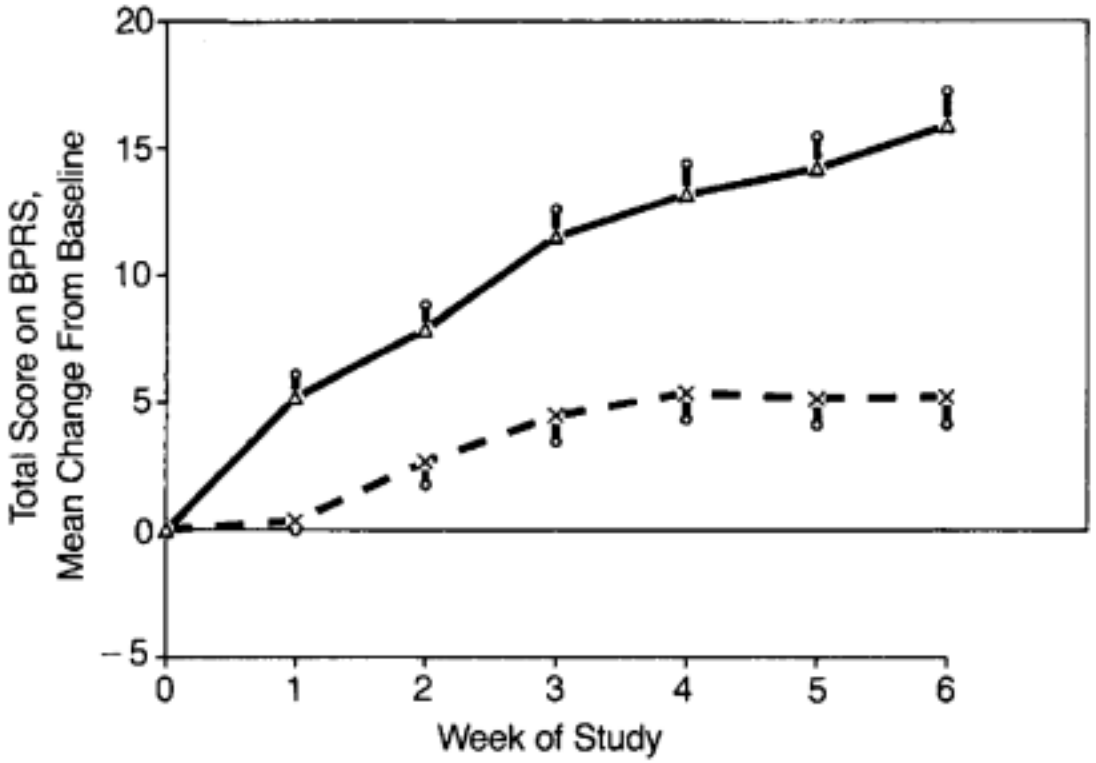

Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P<.001$ during each week of study.

Kane 1988

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FDA APPROVAL AND REMS CREATION

- FDA approved 1989 as a package (CPMS)
  - Sandoz partnered with Caremark (distribution) and Roche (lab)
  - Included lab delivery, lab reporting to provider, med delivery
  - 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

ENDURING EFFICACY

Lancet. 2019 Sep 14;394(10202):939–951. doi: 10.1016/S0140-6736(19)31135-3

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis

Maximilian Huhn [a,*], Adriani Nikolakopoulou [b], Johannes Schneider-Thoma [a], Marc Krause [a,c], Myrto Samara [a], Natalie Peter [a], Thomas Arndt [a], Stefan Leucht [a]

Review > Acta Psychiatr Scand. 2017 Apr;135(4):296-309. doi: 10.1111/acps.12700. Epub 2017 Feb 3.

The impact of clozapine on hospital use: a systematic review and meta-analysis

ajp.bp.115.177261.

R Land [1], D Siskind [2 3], P McArdle [2 3], S Kisely [2 3], K Winckel [1 4], S A Hollingworth [1]

Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis

Dan Siskind [1], Lara McCartney [2], Romi Goldschlager [2], Steve Kisely [2]

WHEN TO USE CLOZAPINE?

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WHEN TO USE TREATMENT RESISTANT SCHIZOPHRENIA

- TRS
  - ~30% of all pts with schizophrenia
  - ~ 10% of FEP within 1 year
- Traditional Parameters
  - Failure to respond to 2 previous antipsychotic trials
  - Usually from 2 separate classes
  - Usual doses for 4-6 weeks OR Max tolerated dose for 4-6 weeks
- Additional Literature Support
  - High risk for suicide

Meltzer 2012 Hasan 2012

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GUIDELINES FOR USAGE

Date	Source	Failure of 2 APs	Suicidal Thoughts and Behaviors	Persistent hostility and violent behaviors	Catatonia, Psychosocial Dysfunction or TD
2009	PORT	✓	✓	✓	
2015	NICE	✓			
2020	APA	✓	✓		
2023	Delphi	✓	2nd Line	2nd Line	✓
2025	INTEGRATE	✓			

Warnez 2014

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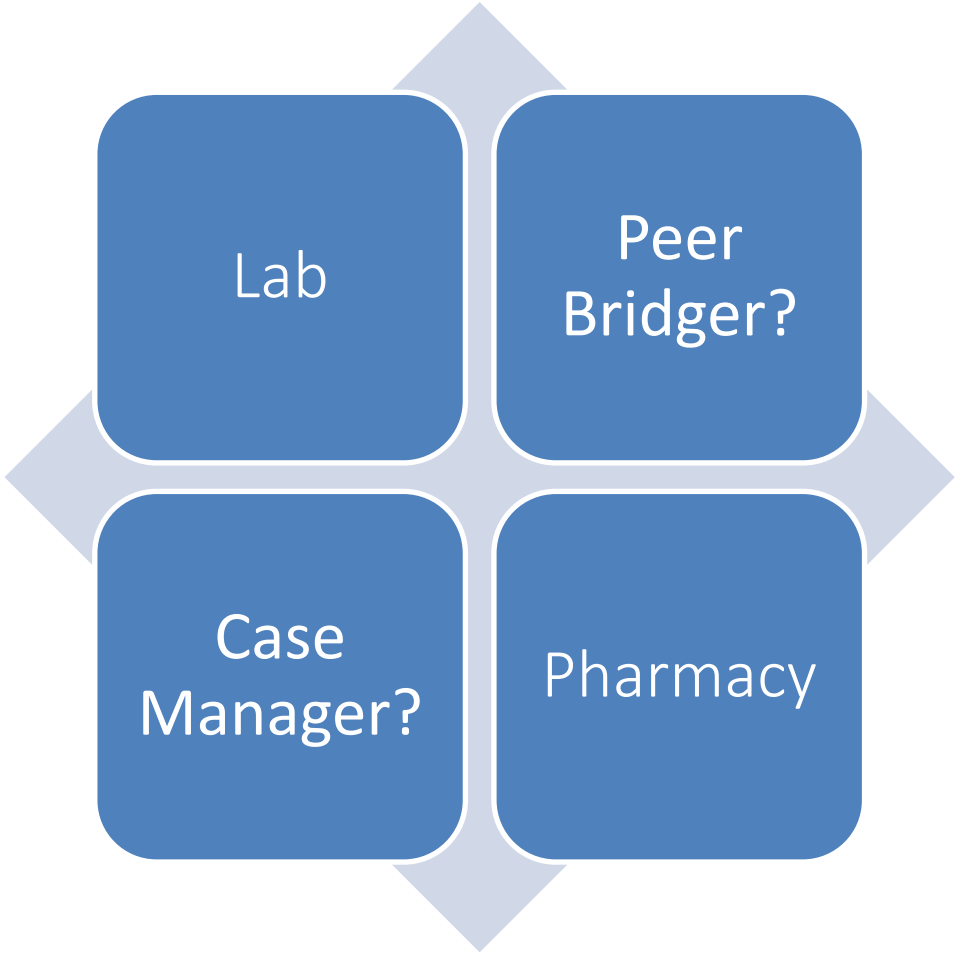
UNDERUTILIZED IN US

- Australia-35%
- China- 30%
- Enlgand-22%
- Sweden-20%
- Germany-20%
- **USA-4%* (2008)**
  - **WA is 27th****

Love 2016 Treatment Advocacy Center* Benito 2023**

PRACTICAL ASPECTS OF USE

- Support for
  - Scheduling/Reminders
  - Transportation



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NAVIGATING REMS CHANGES

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IMPROVING ACCESS: FDA REMS MILESTONES

- 1997: Stable ANC for > 6 months
  - Extension of Q1 Week to Q2 Week monitoring
- 2005: Stable ANC for > 12 months
  - Extension of Q2 Week to Q4 Week monitoring
- 2015:
  - Consolidation of multiple registries into a single registry
  - Interruption in therapy
    - Changed from required for ANC <1500 to ANC <1000
  - New algorithm for those with Benign Ethnic Neutropenia (BEN) adopted

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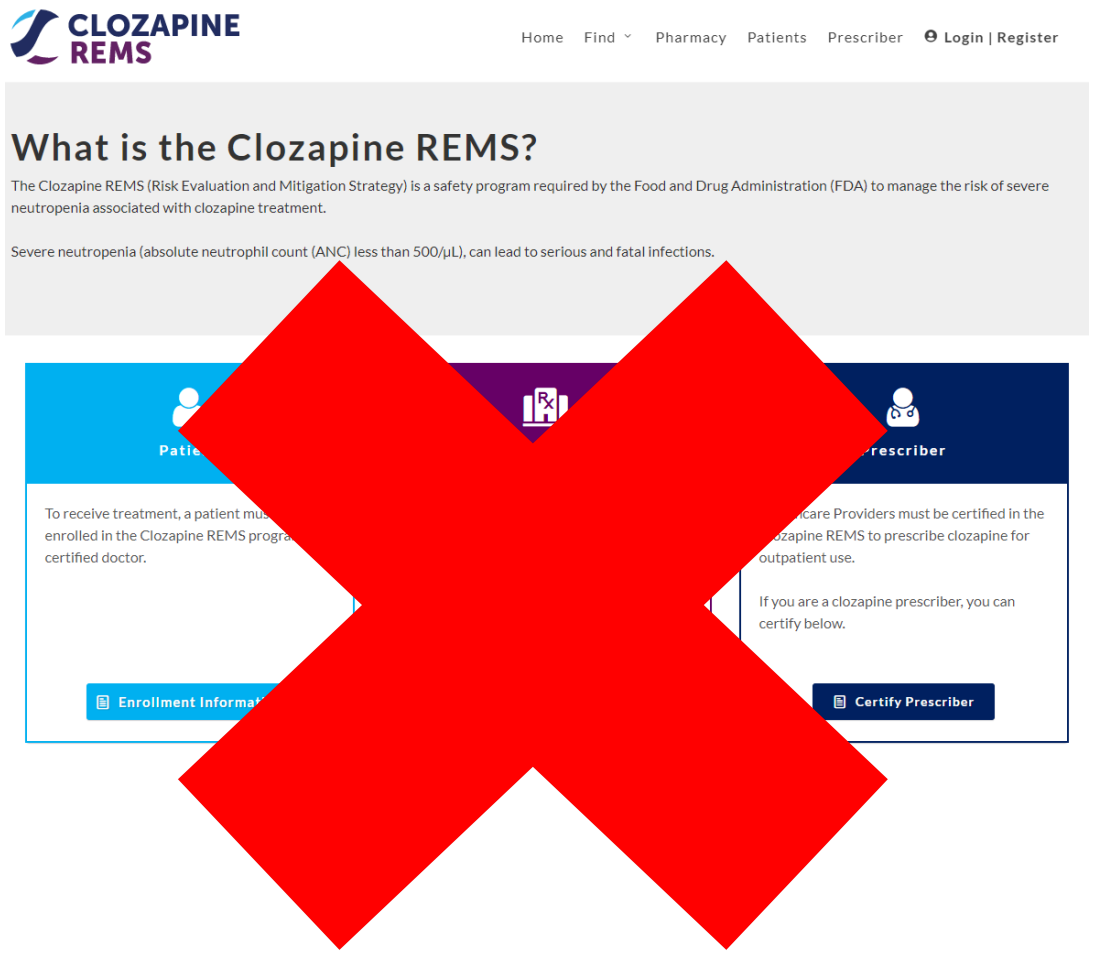
IMPROVING ACCESS: FDA REMS MILESTONES

- 2019 SARS-COV-2 epidemic:
  - "Temporary enforcement discretion"
  - Providers encouraged to use clinical judgment and weigh risks and benefits
- February 2025:
  - Participation in a REMS program regarding ANC is no longer required
  - **FDA continues to recommend ANC monitoring in accordance with prescribing information**

CLOZAPINE REMS AND ANC MONITORING

Prior REMS Requirements for ANC



- Patient Registration
- Prescriber Registration
- Pharmacy Registration

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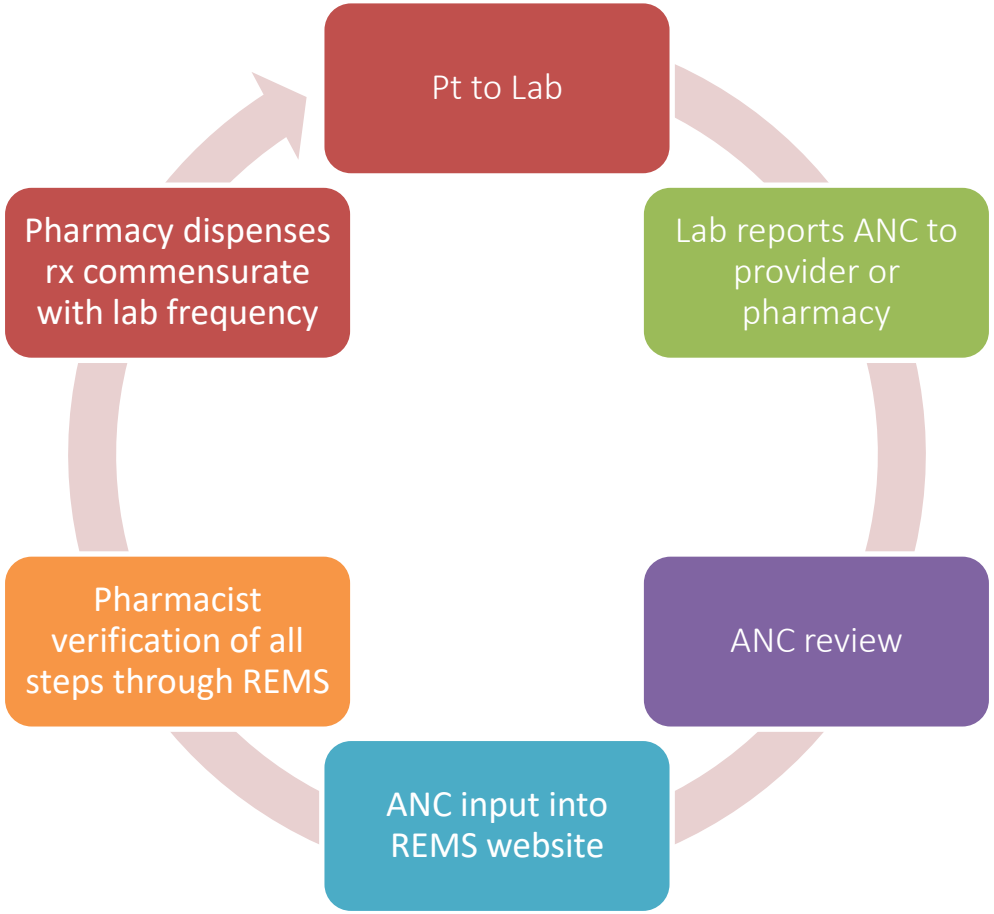
PRIOR REQUIREMENTS OF REMS MONITORING



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INITIATING CLOZAPINE: WHAT *HAS* CHANGED

Interface with REMS

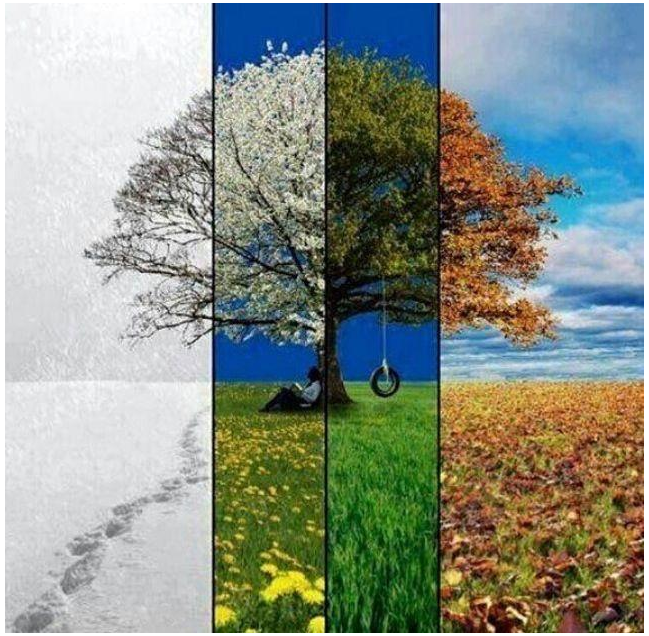
No registration for patient, prescriber, pharmacy

No reporting of ANCs

Prescribe in appropriate increments (7d, 14d, 28d)???

Shift in monitoring responsibility solely to **prescriber**

Informed consent for ANC frequency other than recommended**?**



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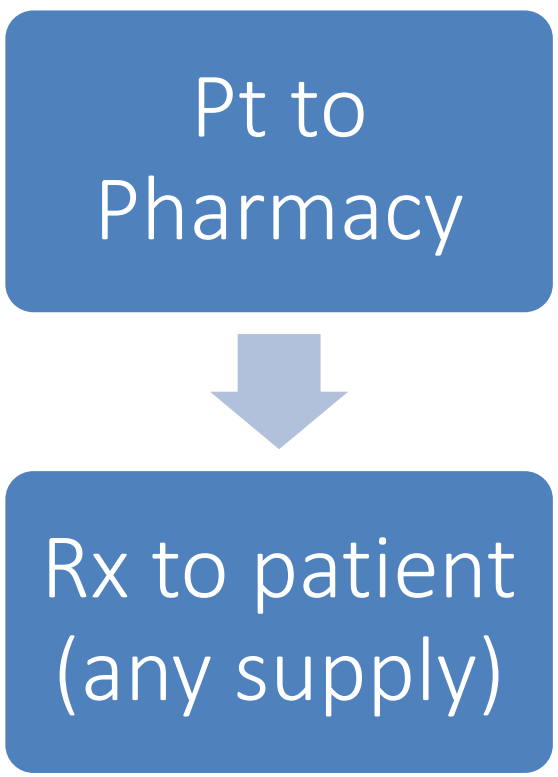
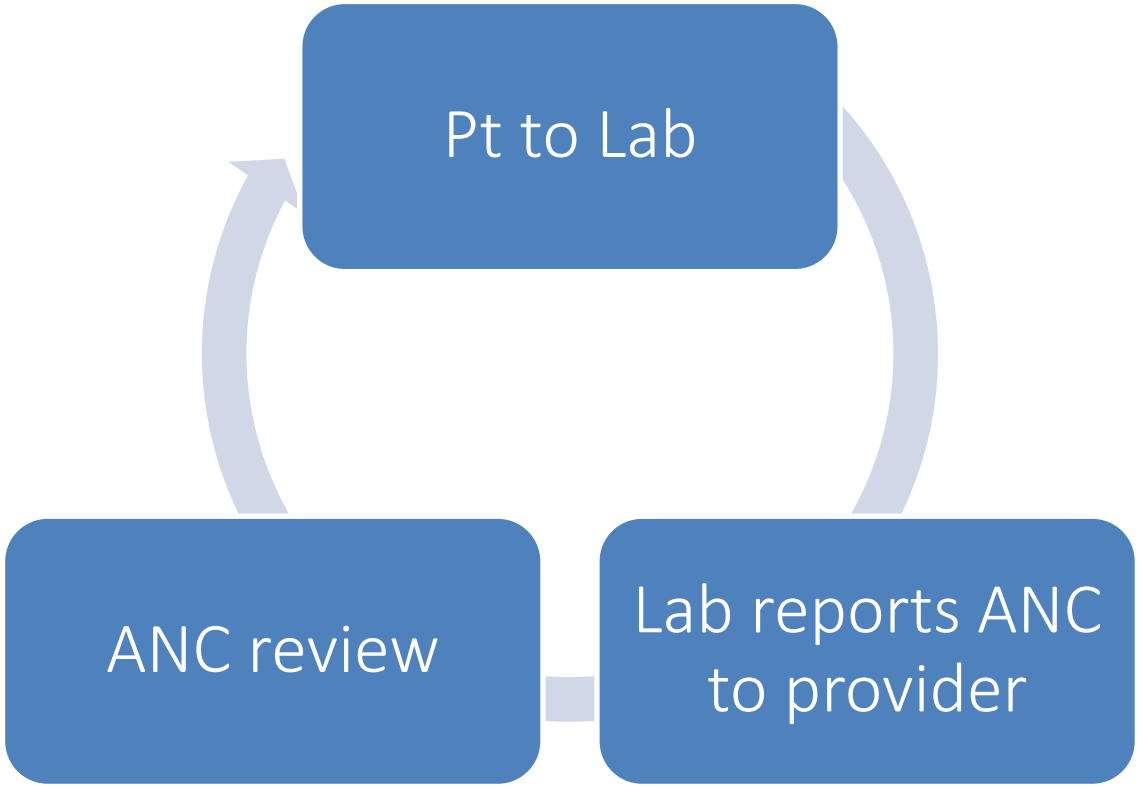
NEW PROCESSES





2015

- No conservation of patient data
  - Former lab values, date ranges, dosages
  - No carryover of the Do Not Rechallenge List

BENEFICIAL REMS COMPONENTS LOST ALONG THE WAY

2025

- No conservation of patient monitoring frequency
  - -Weekly, Q2Weeks, Q4Weeks
  - No prior lab value availability

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CONSIDERATIONS FOR INITIATING CLOZAPINE

What Has Not Changed

- Note smoking status
- Find a lab and Order ANC
- Monitor and manage ADEs

What May Change

- ***Monitor ANCs in accordance with recommended package labelling****
- Delay or slow titrations in relation to lab abnormalities
- Consider Therapeutic Drug Monitoring

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WHAT *MAY* CHANGE

- ANC Monitoring per Prescribing Information
  - US :
    - Weekly x 6 months, Q2 Weeks x 6 months, Q4 Weeks indefinitely
  - EU, Australia, New Zealand:
    - Weekly x 18 Weeks, Q4Weeks indefinitely
  - Canada:
    - Weekly x 26 Weeks, Q2Weeks x 26 Weeks, Q4 Weeks indefinitely

MONITORING

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WORLDWIDE REPORTING OF CLOZAPINE FATALITIES

Order	Deaths	ADR	Lethality
1	2,077	Pneumonia	30%
2	1,449	Cardiac Arrests and Sudden Death	90%
3	550	Agranulocytosis	2%
4	539	Myocarditis	12%
5	326	Constipation	12%

De Leon 2021

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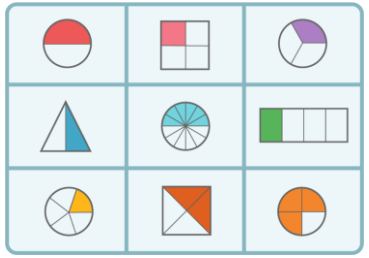
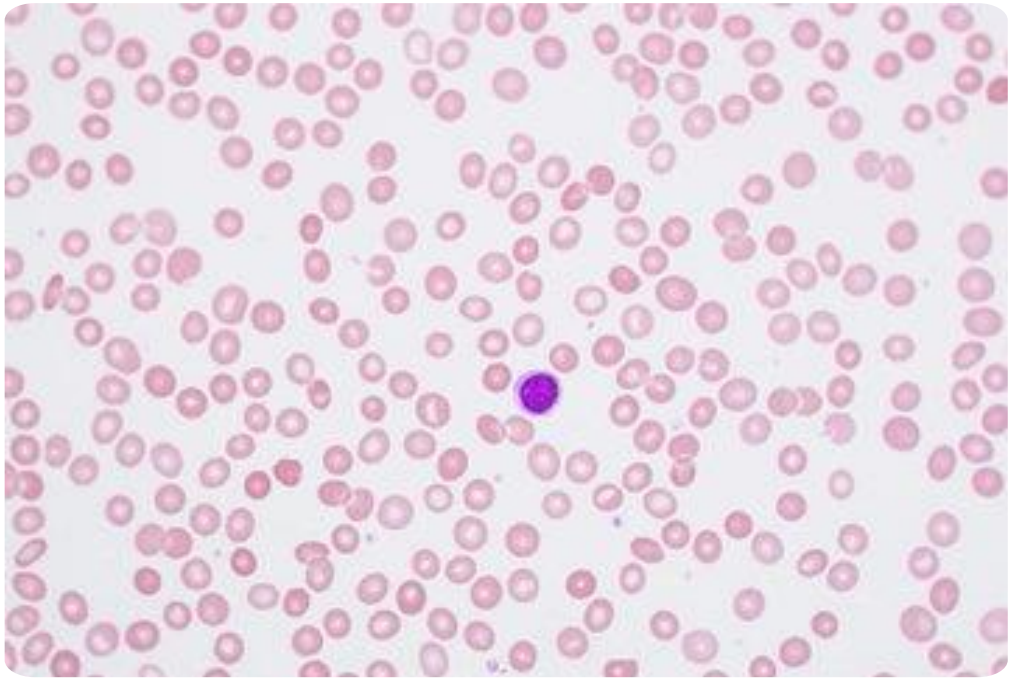
NEUTROPENIA AND AGRANULOCYTOSIS



- Combined risk: 0.7-3.0%
- Neutropenia incidence:
  - 2-3%
- Agranulocytosis incidence:
  - Early data: <0.8%
  - 1990s data: 0.38% in US National Registry Data
  - 2023: 0.47% by Metaanalysis

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

NEUTROPENIA AND AGRANULOCYTOSIS



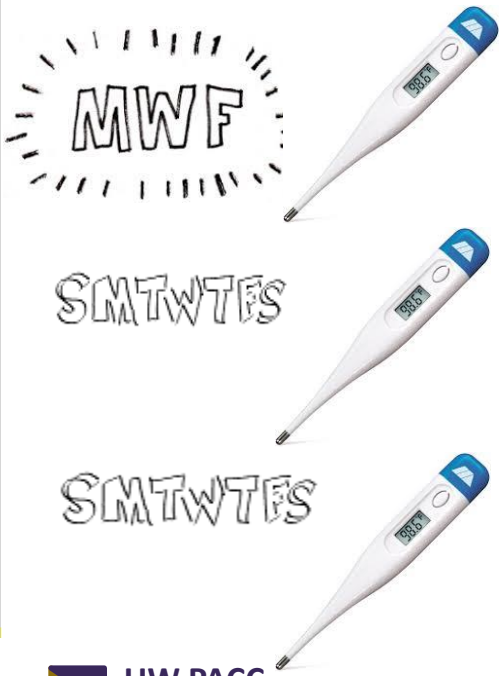
- Dose independent, idiosyncratic??
  - Toxic metabolite
  - Immunologic bone marrow processes
- 2 Subtypes Hypothesized
  - Mild to Moderate (500-1500) with recovery 2-8d (1.8%)
  - Severe (<500) (0.78%)
    - Even when stopped at ANC ~1000, downward ANC progression in 2-5d
    - Lasts 14-21days

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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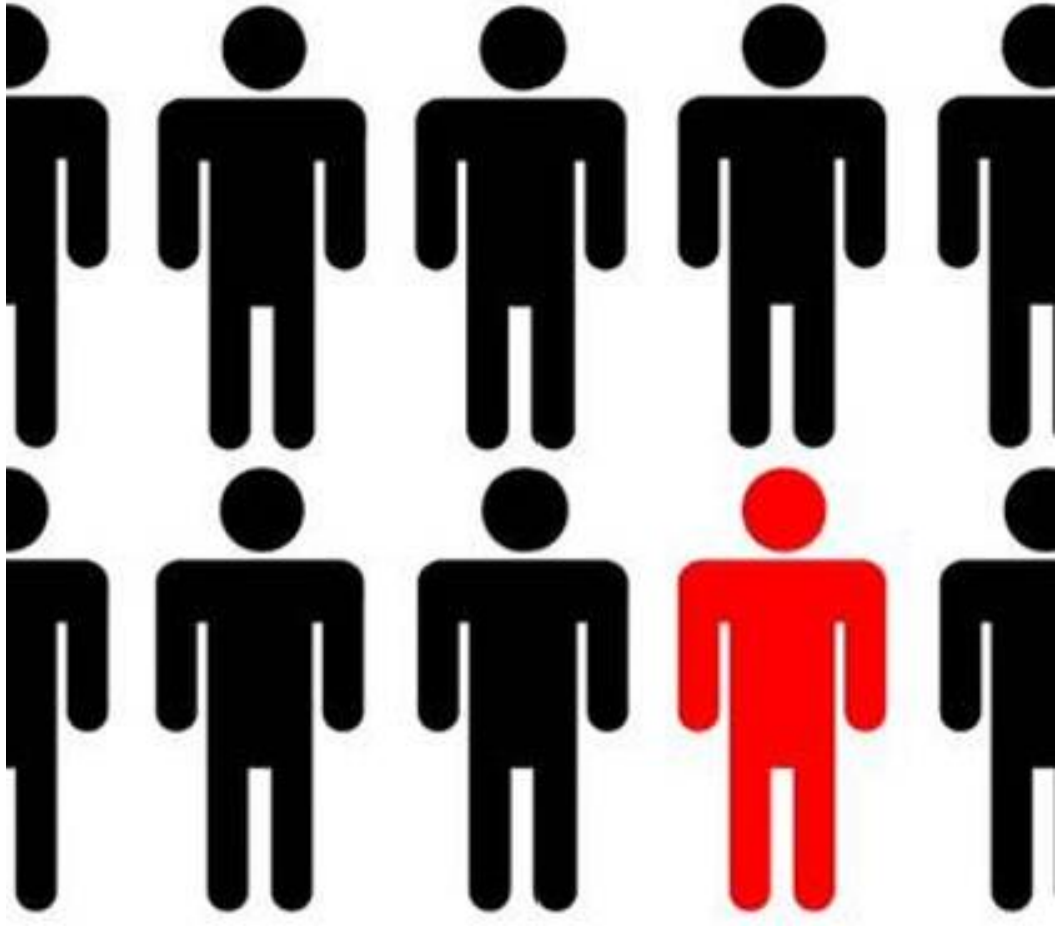
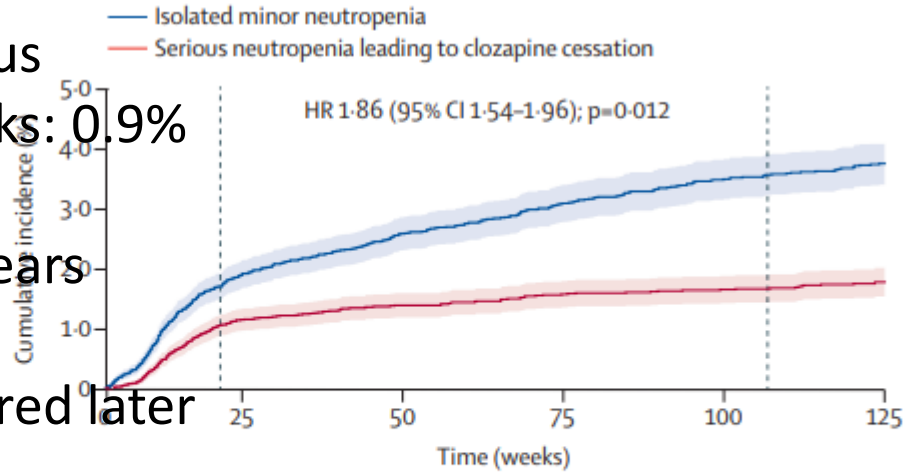
AGRANULOCYTOSIS RISK OVER TIME

Highest risk	First 6-18 weeks Supported by numerous authors in Australian and New Zealand, Chinese, UK/Irish, US and Chilean population samples
Initial ANC monitoring frequencies	Based upon expert opinion and 1 year epidemiological studies
Recent literature	Longer term observational studies suggest lower risk after 2-3 years

Northwood Rubio



- N=26,630 patients from 1990-2022
- Cumulative incidence of serious neutropenic events at 18 weeks: 0.9%
- Progressed to just 1.4% at 2 years
- Very few serious events occurred later than 2 years
- Minor events continuously increased

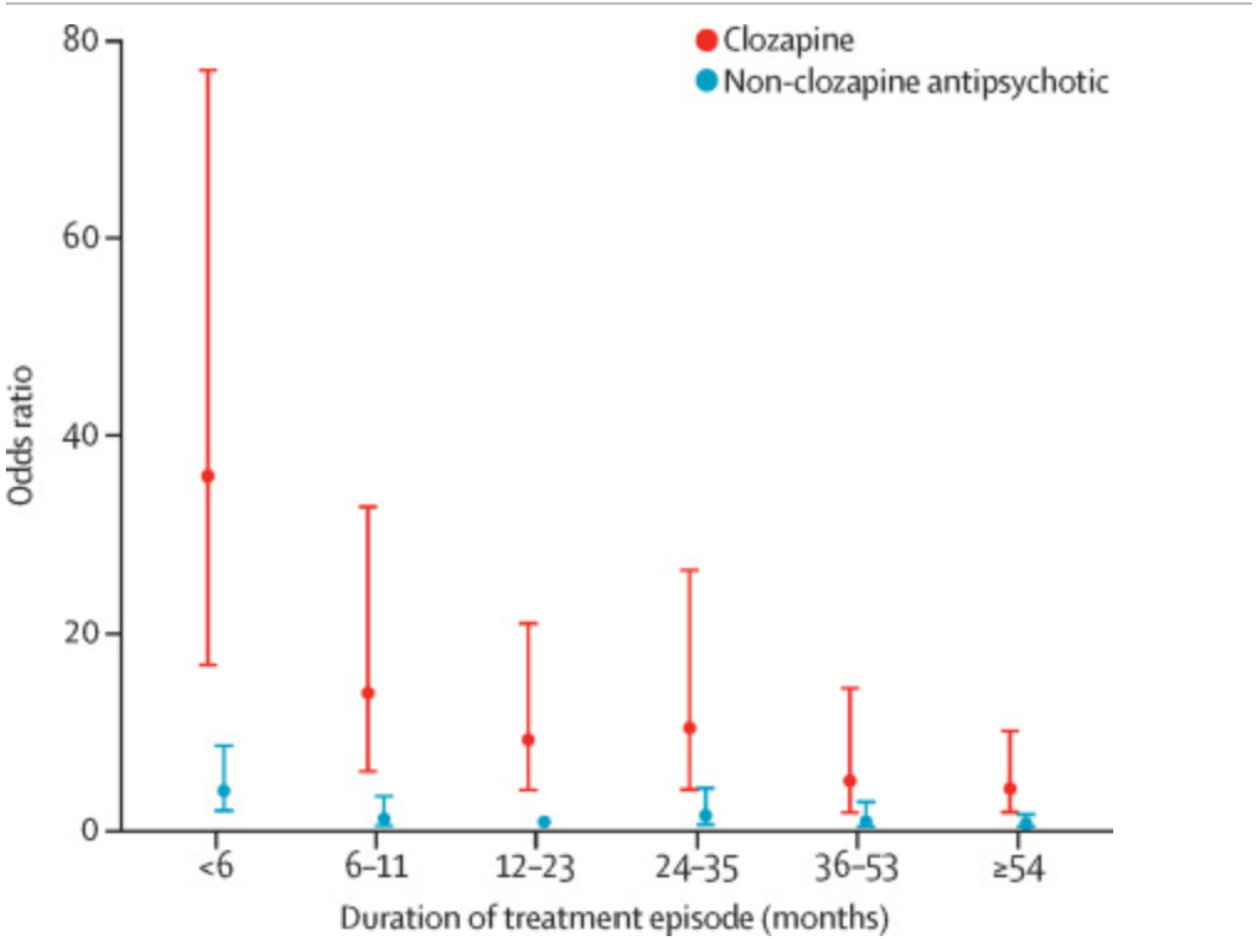


Number at risk	15974	11382	9908	8889	8066	7379
Number censored	418	64	53	41	21	24
Events (cumulative number)						
Minor	3 (3)	2 (270)	1 (338)	1 (386)	1 (421)	0 (441)
Serious	0 (0)	2 (138)	0 (154)	0 (169)	1 (174)	2 (182)

UW PACC Northwood

Finland: Agranulocytosis over 22 years

- N= 61,769 patients, 14,037 clozapine and 47,732 non-clozapine
- Within the clozapine group, highest risk with initial use
  - At 6 months: aOR 36.01 (95% CI 16.79-77.22)
  - At 54months+: aOR 4.38 (95% CI 1.86-10.34)
- Non-clozapine use also highest risk during initial 6 months:
  - At 6 months aOR 4.23 (2.02-8.88)
  - At 54 months+ aOR 0.71 (0.28-1.78)
- **Clozapine and non-clozapine risk begin to overlap at 24-35 months**



ADDITIONAL INSIGHTS

Australia/Aotearoa NZ

- Prior exposure to clozapine led to lower likelihood of minor neutropenia
  - OR 0.59, p<0.00001
- Authors hypothesize that 2y of clozapine tx may obviate need for future monitoring

Finnish

- Additional risk factors:
  - Cancer
  - Concomitant benzodiazepines and mood stabilizers
  - Cardiovascular disease
  - Combination with an added antipsychotic
  - Dose

Northwood Rubio

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UK ANC EXTENDED INTERVAL MONITORING

- Mirror image study from April 2020-July 2021 study
  - 459 patients were monitored Q12W v 110 patients monitored Q4W
- Nonsignificant findings in rates of difference in hematologic events
- 2 patients reverted to Q4W (SARS CoV2, >12W monitoring exceeded)

Group	Mild to Moderate Neutropenia* (n)	Severe Neutropenia	Pre Index Hospitalizations*	Post Index Hospitalizations*
Q4W	0.4% (2)	0	52%	60%
Q12W	0.9% (1)	0	55%	60%

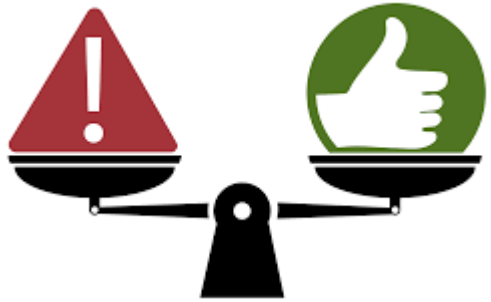
*Findings did not reach statistical significance

US ANC EXTENDED INTERVAL MONITORING

- Conducted during the SARS CoV2 pandemic
- Retrospective VA study involving 2,106 patients
- Comparison of ANC gaps (<30d, 30-60d, 60-90d, 90-180d, >180d)
  - No significant differences in neutropenic events
- Comparison of rx discontinuation rates and gaps in ANC monitoring
- Patients adhering to Q1 month monitoring with highest rates of d/c
- Patients monitored Q2 months: 49% less likely to d/c*
- Patients monitored Q3 months: 31% less likely to d/c*

*Statistically significant

ESTIMATES OF RISK VERSUS BENEFIT



Agranulocytosis Risks

Older data

- Risk of death from agranulocytosis US National Registry Data = 0.012%

Newer data

- Risk of death from agranulocytosis from observational study in Iceland= 0.02%

In sum

- 1-2 deaths per 10,000

Benefits in Suicide Reduction

Older data

- InterSePT trial
  - 24% reduction in suicide attempts compared with olanzapine

Newer data

- Tiihonen
  - Risk for suicide with clozapine was 0.34 compared to 1.0 for perphenazine and 1.58 for quetiapine

Meltzer 2012 Ingimarsson Meltzer 2003

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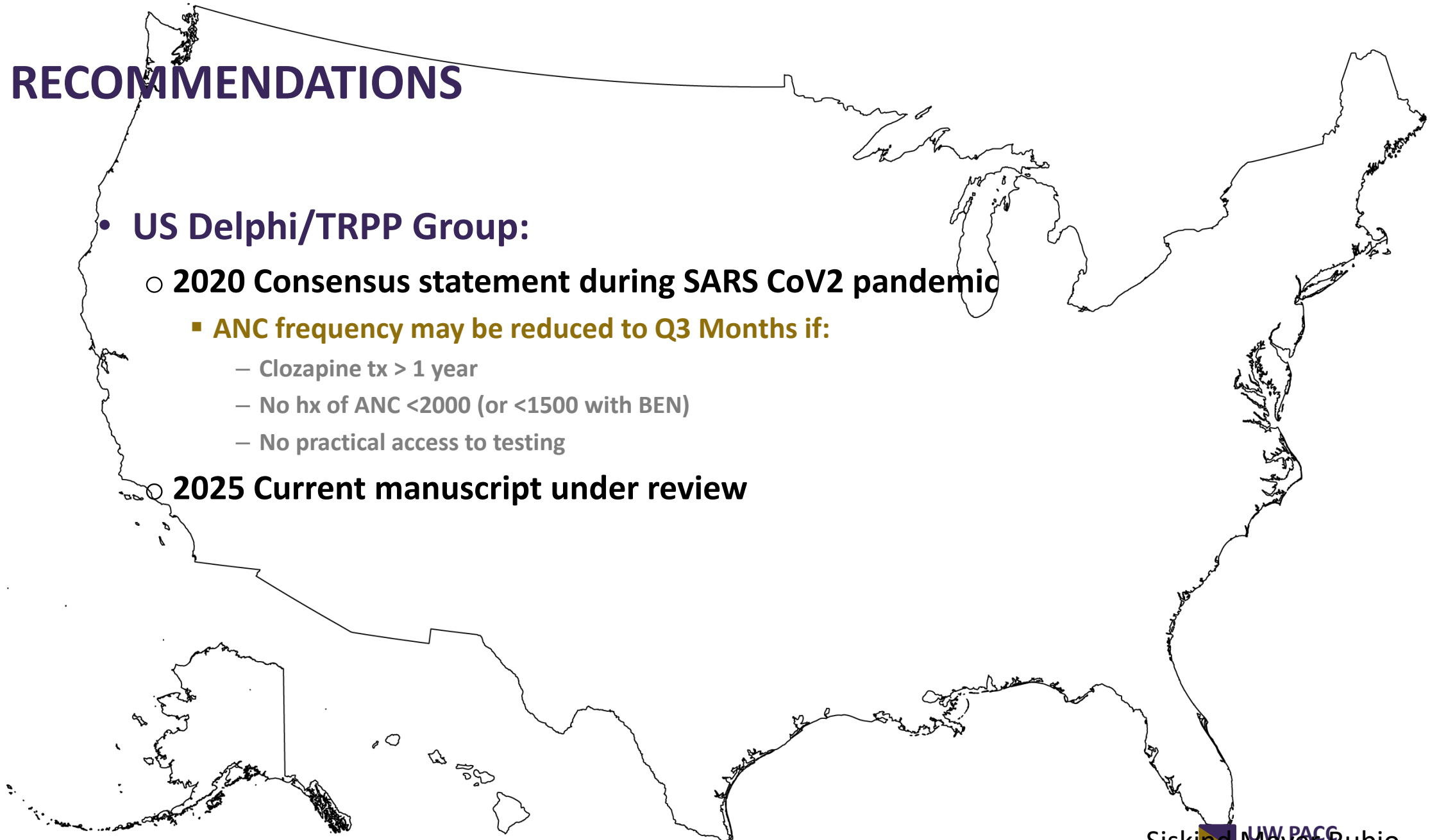
INTERNATIONAL RECOMMENDATIONS

- Finnish: Weekly x 6 months, Q2W x 6-12 months, Q4W for Years 1-3, Cessation
- EU: Weekly x 18W, Q4W through 1 year, Quarterly through 2 years, then Annually
- **Chile: Weekly x 18W, Q4W through 1 year, Q2 months afterwards "at most"
- Dutch: Weekly x 18W, then Shared Decision Making

**Already in effect

Meyer and Rubio

US RECOMMENDATIONS



- **US Delphi/TRPP Group:**
  - **2020 Consensus statement during SARS CoV2 pandemic**
    - **ANC frequency may be reduced to Q3 Months if:**
      - Clozapine tx > 1 year
      - No hx of ANC <2000 (or <1500 with BEN)
      - No practical access to testing
  - **2025 Current manuscript under review**

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De Leon 2021

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CLOZAPINE ASSOCIATED MYOCARDITIS

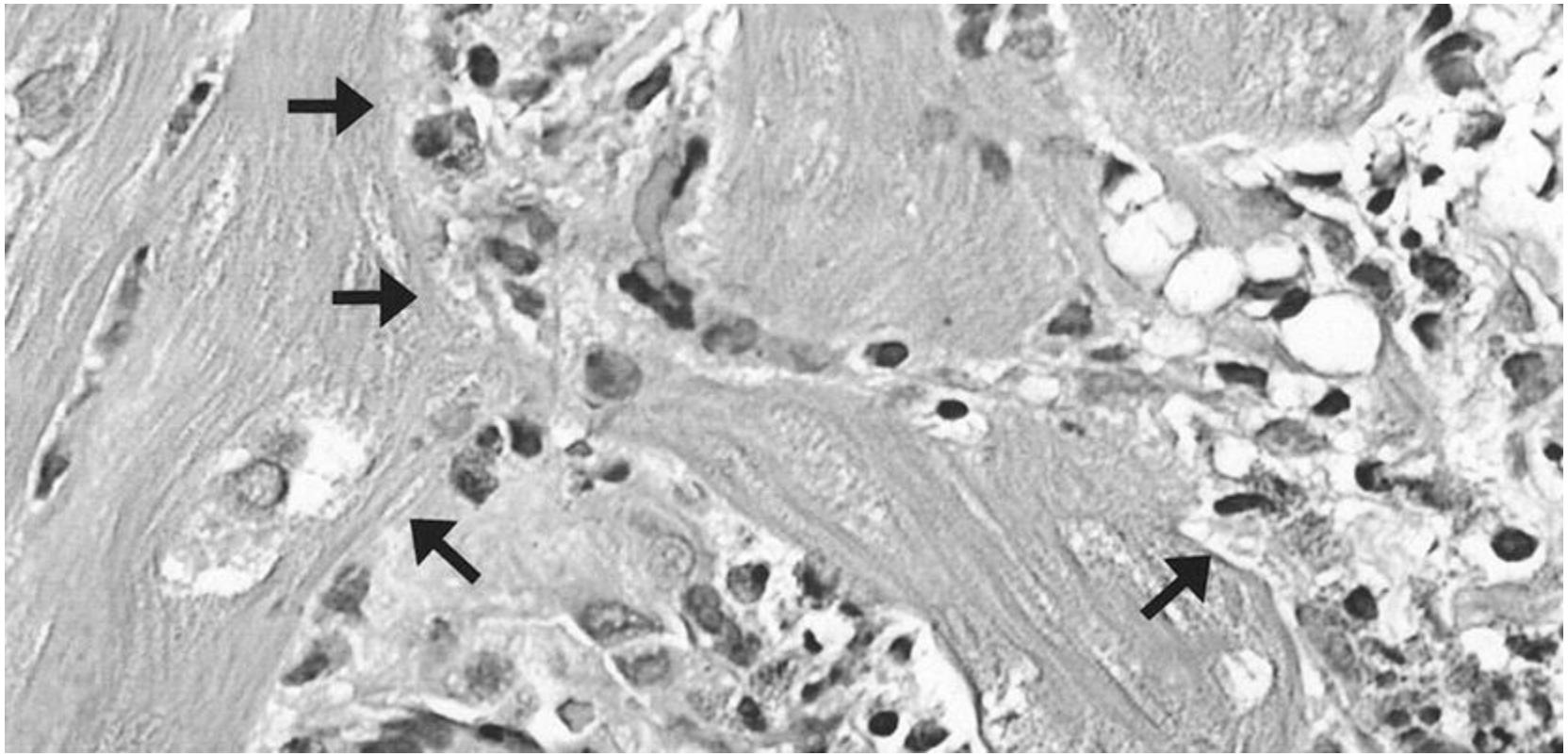

Image by Pieroni M et al. Chest 2004;126: 1703-1705.

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CAM: BASICS

Risk

- Worldwide estimates of 0.1% to 2%
- Higher rates in Australian samples
  - 1.5-8%
- Mortality
  - Up to 50%
- Carries a Black Box Warning within US
- Rechallenge
  - Generally not recommended, considered on an individual basis

CAM: BASICS

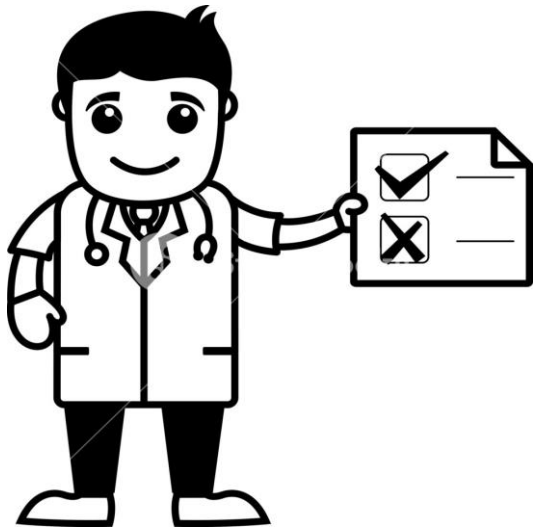
Risk Factors

- Male
- Younger Age
- Aggressive Titrations?
- Concomitant Medications?
  - Divalproex?

CAM: PRESENTATION

- Nonspecific sx:
  - Tachycardia, palpitations
  - Hypotension
  - ECG changes
  - Chest pain
  - Dyspnea
  - Fever, other flu like sx
  - Fatigue
  - Malaise
  - Diarrhea

- Hypothesized Phases:
  - Prodromal
    - Frequent fever
    - Inflammatory cytokine release
      - May impede metabolism
  - Local Inflammation
    - Pancreatitis, Myocarditis, Nephritis



Ronaldson, De Leon

CAM: PRESENTATION AND MONITORING

- Timeframe:
  - First 4 weeks of treatment
    - Majority of cases
  - First 8 weeks of treatment
- Management
  - Clozapine cessation
  - Supportive care
  - **Early detection?**

- Monitoring Recommendations
  - Not overtly suggested by prescribing information
  - Delphi group
    - "Guidance" versus "Nonconsensus"
  - Recommended by prominent authors
    - De Leon
    - Ronaldson
  - Recommended by Metaanalysis
  - Performed at some US facilities

Ronaldson De Leon Wagner Leung

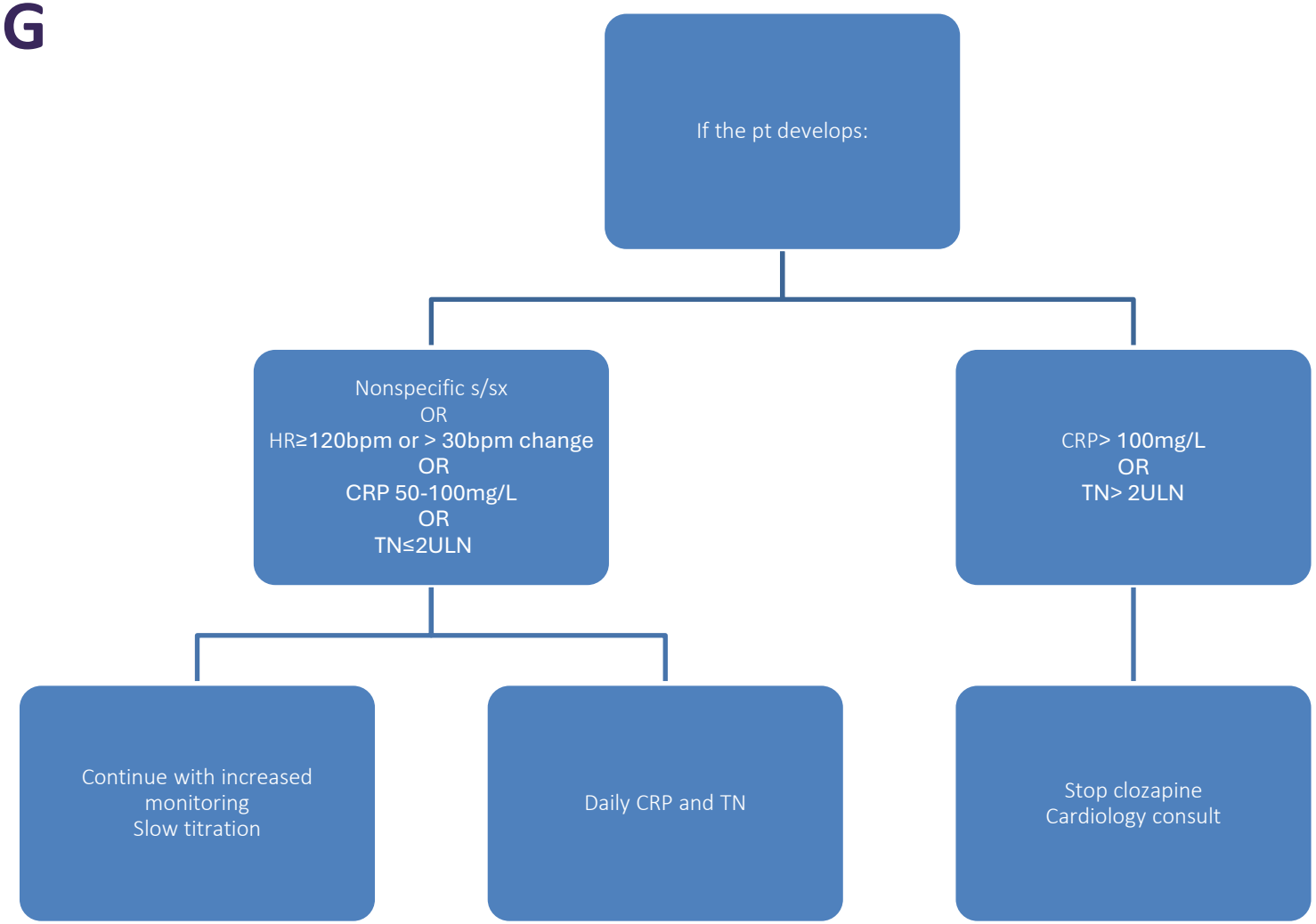
UW BACC

CAM: PREVENTIVE MONITORING

Daily	• Nonspecific sx: Chest Pain, Dyspnea, GI sx
Every other Day	• BP, HR (tachycardia), RR, Temperature
Baseline and Weekly	• CRP • Troponins • Eosinophilia

AUSTRALIAN MONITORING

- Prescribing information
  - Recommends myocarditis lab monitoring parameters
  - Allows for faster dosing titrations



Ronaldson and Carswell

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PHARMACOKINETICS:

-RECONSIDERING TITRATIONS

-CONSIDERING DRUG LEVEL MONITORING

-DRUG INTERACTIONS

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HISTORIC TITRATION INPATIENT SCHEDULES

- Usual starting dose is 25mg HS (12.5mg HS for select patients)
- Increase by 25mg/d with weighted doses at HS
- Initial target dose is usually 300-350mg/d
- Provided in 25mg tablets, 50mg, 100mg tablets
- Usually use 25mg tabs while titrating
  - Avoid half tabs…..
  - Think in terms of tabs per day

ORIGINAL 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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OUTPATIENT TITRATION SAMPLES: NHS 2024

Week 1			
Day	AM	PM	Total mg
1	-	6.25	6.25
2	-	12.5	12.5
3	6.25	12.5	18.75
4	6.25	25	31.25
5	12.5	25	37.5
6	12.5	25	37.5
7	12.5	50	62.5

Week 2			
Day	AM	PM	Total mg
1	12.5	50	62.5
2	12.5	50	62.5
3	12.5	75	87.5
4	12.5	75	87.5
5	25	75	100
6	25	75	100
7	25	100	125

End of Week 3	Total mg
	200

End of Week 4	Total mg
	275

[Clozapine outpatient titration updated Jan 2024.pdf]

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OUTPATIENT TITRATION SAMPLES: NETHERLANDS

Clozapine titration scheme for outpatients

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Clozapine in mg	2x6.25	12.5	25	25	37.5	50	50	62.5	62.5	62.5	75	75	100	100	100	100	100*

Clozapine titration scheme for inpatients

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Clozapine in mg	2x6.25	25	50	75	100	100	100	100	150*	200	200	200	200	200*

[Clozapinepluswerkgroep]

*Denotes suggestions for TDM

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NEW CONSIDERATIONS: TITRATION BY CRP

- De Leon et al.
  - Acknowledges nonspecific nature of CRP elevation
  - Baseline CRP:
    - If elevated, rule out any infection before initiation
  - CRP Elevations during titration
    - Clozapine induced inflammation may lead to CYP enzyme inhibition, slower metabolism
    - Possible identification of a poor metabolizer
    - Consider slowing titration
- Delphi Working Group
  - References De Leon et al and states that slower titration in event of CRP elevations may minimize ADRs

De Leon Wagner

INPATIENT ANCESTRY BASED TITRATION

Ancestry	Initial Dose (per day)	Dose Titration (per day)	Likely Target Dose for a female non-smoker (per day)	Likely Target Dose for a male smoker (per day)
Asian or Original people from the Americas	12.5mg	12.5-25mg	175mg	300mg
European/Western Asian	25mg	25-50mg	250mg	400mg
US (European or African ancestry)	25mg	25-50mg	300mg	600mg

INPATIENT ANCESTRY BASED TITRATION FOR THOSE WITH LOWER METABOLISM OR DRUG INTERACTIONS

Ancestry	Initial Dose (per day)	Dose Titration (per day)	Likely Target Dose for a female non-smoker (per day)	Likely Target Dose for a male smoker (per day)
Asian Original people from the Americas	6.25mg	6.25-12.5mg	75mg	150mg
European/Western Asian	12.5mg	12.5-25mg	100mg	200mg
US (European or African ancestry)	12.5mg	12.5-25mg	150mg	300mg

THERAPEUTIC DRUG MONITORING (TDM)

- Utility of monitoring
  - Accuracy of ensuring levels above the minimum therapeutic threshold (350ng/ml)
  - Ensure adherence
  - Detect potential for toxicity
    - Infection, may require dose decreases by up to 1/3
- Pitfalls of monitoring
  - Responsive dose decreases may lead to decompensation
  - Inter- and intra- patient variability

ADEQUATE CLOZAPINE TRIALS

Date	Source	Guidance
2009	PORT	With inadequate response, obtain a clozapine level to ensure it is >350ng/ml
2015	NICE	With inadequate response, consider TDM before adding a second agent
2020	APA	With inadequate response, dose should be increased to attain a level >350ng/ml
2023	Delphi	Levels >350ng/ml for 12 weeks
2025	INTEGRATE	12 week trial at >350ng/ml

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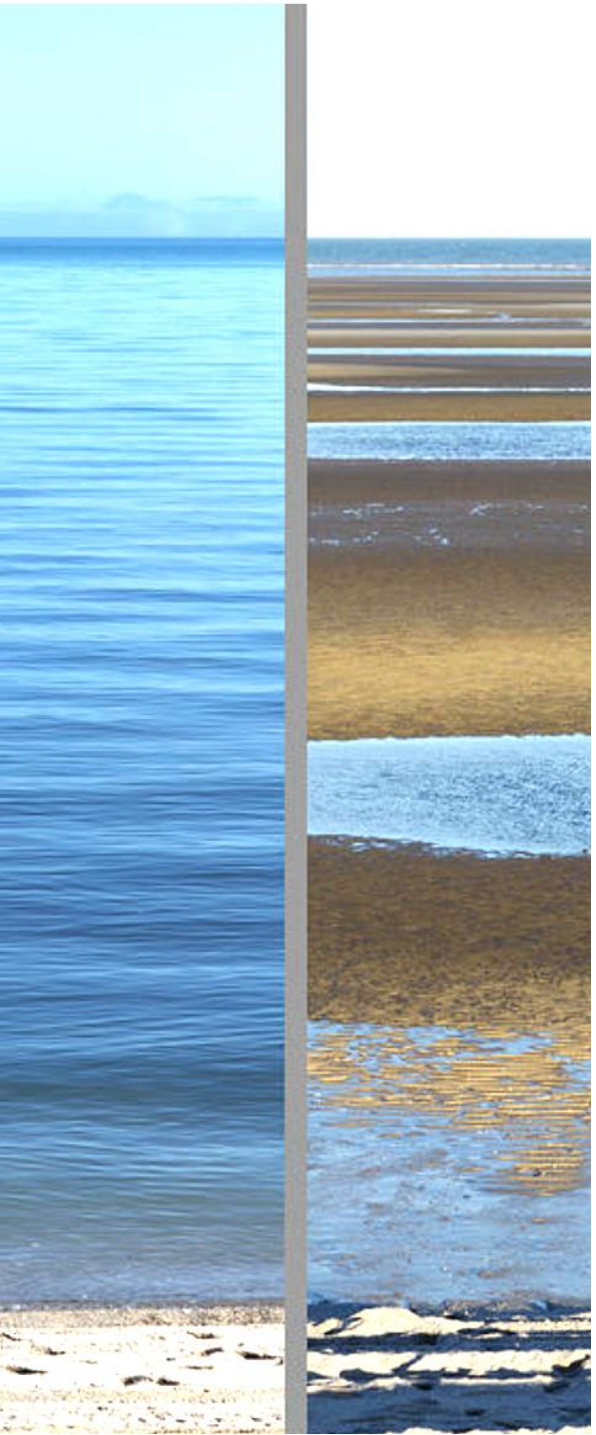

TDM: OLD LEVELS

Lower Limit

- 350ng/ml
  - 1990s studies
    - Demonstrated greater percentages of patient response
    - Multiple authors consistently noted similar results

Upper Limit

- 1,000ng/ml
  - Often listed as ULN historically
  - Based upon 3 early case reports noting seizures and delirium
  - Disagreement between early literature regarding the upper limit
    - EEG changes at normal doses
    - Dose related risk for seizure

TDM: NEW LEVELS

- 2023 Metaanalysis:
  - Included 294 patients and changes in BPRS
    - Optimal response ~370 ng/ml
    - NNT for interquartile range of ~250ng/ml-550ng/ml= 5.5
    - NNT for >550ng/ml= 17.2

- 2021 Review and Metaanalysis
  - Included 380 patients, 696 patients, and changes in BPRS
  - Higher rates of response for levels >350ng/ml, OR 2.27 ($p< 0.001$)
    - Also found NNT 5
  - At levels >600ng/ml, no significant difference OR 1.4 ($p=0.19$)
    - NNT 8.4
  - ***600ng/ml listed as new UNL for most labs***

TDM AND DELPHI TRRIP CONSENSUS

Treatment Stage	Recommendation
Initiation	During initial 4 weeks After stable dose attained Poor response
Ongoing	Worsening symptoms Change in smoking Drug interaction Infection Dose dependent side effects Symptoms of toxicity

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VISUALIZING DRUG INTERACTIONS

- Clozapine metabolism
  - CYP3A4= 70%
  - CYP1A2= 15%
  - CYP2C19= 5%
  - Remainder
    - CYP2D6
    - CYP2C9
    - CYP2C8
    - FMO3

- CYP1A2 Potent ***Inhibitors***
  - Fluvoxamine
  - Ciprofloxacin

Clozapine

CYP ***Inhibitor***

VISUALIZING DRUG INTERACTIONS

- Clozapine metabolism
  - CYP3A4= 70%
  - CYP1A2= 15%
  - CYP2C19= 5%
  - Remainder
    - CYP2D6
    - CYP2C9
    - CYP2C8
    - FMO3

- CYP1A2 ***Inducers***
  - Carbamazepine
  - Phenytoin
  - Tobacco smoking
  - Rifampin
  - Omeprazole (weak)

Clozapine

CYP ***Inducer***

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DRUG INTERACTIONS

+

CYP1A2 Inducer

Up to ~~ 30-50% Lower Clozapine Levels!

-as few as 5 cigarettes

CYP1A2 Inhibitor

2x-5x Higher Clozapine Levels!

Tsuda 2013

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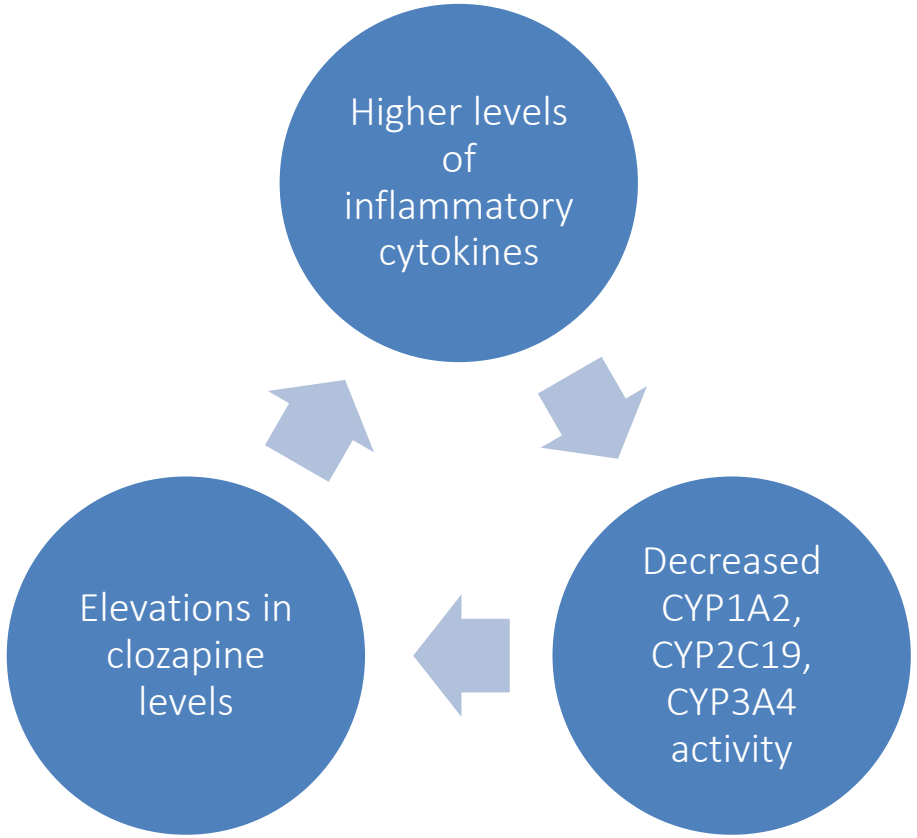
LESS WELL DOCUMENTED DRUG INTERACTIONS

- Estrogen containing oral contraceptives
  - Moderate CYP1A2 Inhibitor
    - Case reports with TDM demonstrate that interaction may be significant
- Caffeine
  - Moderate CYP1A2 Inhibitor
    - Caution in those consuming >1 cup coffee per day or significant changes in caffeine intake
- Valproate
  - Inhibitor and Inducer?
  - Variable complex, timing dependent inhibitory effects
    - May act as an inhibitor during early titration, an inducer later in tx
    - Competitive inhibitor in nonsmokers (~15% increase in clozapine levels)

DRUG DISEASE STATE INTERACTIONS

- Infection
  - Based upon observational studies
    - ~ 10% required no dose adjustment
    - ~30% required reduction by 1/3
    - ~60% required reduction by ½
  - Similar dose adjustments suggested in tertiary drug info references
  - Consider TDM



DRUG DISEASE STATE INTERACTIONS

- Obesity
  - Less well documented
  - BMI>29 may be associated with a decrease in clozapine metabolism
  - Lipophilicity versus increased inflammation or combination

CONCLUSIONS: FEWER BARRIERS AND SAFER USAGE

- 30% of patients have TRS
- Anticipate changes in ANC monitoring frequencies beyond 2 years duration
- Prophylactic lab monitoring for myocarditis
  - Weekly Troponin and CRP during initial 4-8 weeks
- Personalized Titrations
  - Aided by Baseline and weekly CRP values
  - Guided by ancestry or Pharmacogenetic testing
- Therapeutic Drug Monitoring
  - Minimum > 350ng/ml, between 350-600ng/ml for most and >600ng/ml for some

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REFERENCES

- Benito RA, Gatusky MH, Panoussi MW, et al. Thirteen fold variation between states in clozapine prescriptions to united states medicaid patients. Schizophr Res. 2023 May;255: 79-81. RESEARCH WEEKLY: Hurdling the clozapine barriers - Treatment Advocacy Center
- Buchanan RW, Kreyenbuhl J, Kelly DL, et al. Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93.
- Carswell O, Wilton LR, Nicholls K, et al. A 12 month audit of clozapine associated myocarditis in South Australian Local Health Network: the importance of screening and personalised titration. *Schizophr Res*. 2024;268: 88-93.
- De Leon J, Schoretsanitis G, Smith RL, et al. Guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP and clozapine levels. *Pharmacopsychiatry* 2022;55: 73-86.
- Food and Drug Administration. Joint meeting of the drug safety and risk management advisory committee and the psychopharmacologic drugs advisory committee. (November 2024). November 19, 2024 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee. https://www.dfda.gov/media/183655/download.
- Greenwood-Smith C, Lubman DI and Castle DJ. Serum clozapine levels: a review of their clinical utility. *J Psychopharmacol*. 2003;**17(2):234-238.**
- Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*. 2012;13(5): 318-378.
- Honigfeld G, Arellano F, Sethi J, et al. Reducing clozapine related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry*. 1998;59(suppl.e):3-7.
- Howes OD, McCutcheon R, Agid O, et al. Treatment resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry.2017;174(3):216-229.

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REFERENCES

- Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi episode schizophrenia: a systematic review and network meta analysis. *Lancet* 1019; 394: 939-951.
- Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment resistant schizophrenic: a double blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45(9):789-796.
- Kelly DL, Freudenreich O, Sayer MA and Love RC. Addressing barriers to clozapine utilization: a national effort. *Psychiatr Serv.* 2017;69(2): 224-227
- Kelly DL, Ben-Yoav H, Payne GF, et al. Blood draw barriers for treatment with clozapine and development of a point of care monitoring device. Clin Schizophr Relat. Spring 2018;12(1):23-30.
- Little AL, Maister AJ, Ash LR, et al. Implications of clozapine monitoring during the covid-19 pandemic. *Psychiatric Serv*. 2025; Apr 30 doi: 10.1176/appi.ps.20240456.
- Leung JG, Zhang L, Markot M, et al. A systematic review of clozapine associated inflammation and related monitoring. *Pharmacother*. 2023;43:1364-1396
- Love RL, Kelly DL, Freudenreich O, and Sayer MA. 2016 Sept Clozapine underutilization: addressing the barriers. National Association of State Mental Health Program Directors Alexandria, VA. https://www.nasmhpd.org/content/tac-assessment-working-paper-clozapine-underutilization-addressing-barriers
- Matistri C, Mellini C. Clozapine associated agranulocytosis: a systematic review. Is it really so frighteningly common? *J Clin Psychopharmacol*. 202343(6):527-533.
- McCutcheon, R, Pilinger T, Varvari J, et al. INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia. *Lancet Psychiat*. 2025;12:384-394.
- Meltzer HY, Alphs L, Green AI, et al. International suicide prevention trial study group. Clozapine treatment for suicidality in schizophrenia: International suicide prevention trial (InterSePT). *Arch Gen Psychiatry* 2003;60(1): 82-91.
- Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. *Clin Schizophr Relat* 2012 Oct;6(3):134-44.

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REFERENCES

- Meyer JM and Rubio JM. Clozapine monitoring in the post-REMS world: some guidance for clinicians. J Clin Psychiatry 2025;86(2): 25ac15898
- Northwood K, Pearson E, Arnautovska U, et al. Optimising plasma clozapine levels to improve treatment response: an individual patient data metaanalysis and receiver operating characteristic curve analysis. *Br J Psychiatry* 2023;222: 241-245.
- Oloyede E, Olubanke D, Abolou Z, et al. Clinical impact of reducing the frequency of clozapine monitoring: controlled mirror image cohort study. Br J Psychiatry. 2023 Aug;223(2): 382-388.
- Ronaldson KJ, Fitzgerald PB, McNeil J, et al. A new monitoring protocol for clozapine induced myocarditis based on an analysis of 75 cases and 94 controls. *ANZJP* 2011;45(6) 458-465.
- Siskind D, Sharma M, Pawar M, et al. Clozapine levels as a predictor for therapeutic response: a systematic review and metaanalysis. *Acta Psychiatr Scand.* 2021 Nov;144(5):422-432.
- Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the covid-19 pandemic. J Psychiatry Neurosci. 2020 May 1;45(3):222-223
- Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11 year follow up of mortality in patients with schizophrenia: a population based cohort study (FIN11 study) 2009 Aug 22;347(9690)629-7.
- Tsuda Y, Saruwatari J, Yasui Furukori N. Metaanalysis: the effects of smoking on the disposition of two commonly used antipsychotic agents. *BMJ Open.* 2014;4: e004216. doi:10.1136/bmjopen-2013-004216.
- Wagner E, Siskingd D, Falkai P, et al. Clozapine optimization: A Delphi consensus guideline from the treatment response and resistance in psychosis working group. *Schizophr Bull*. 2023;49(4): 962-972.
- Warnez S and Aless-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psych 2014 Apr 7;14:102.

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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

REFERENCE MATERIALS

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

NEUTROPENIA AND AGRANULOCYTOSIS

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

MANAGEMENT OF NEUTROPENIA/AGRANULOCYTOSIS

- 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

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

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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%

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)*

- 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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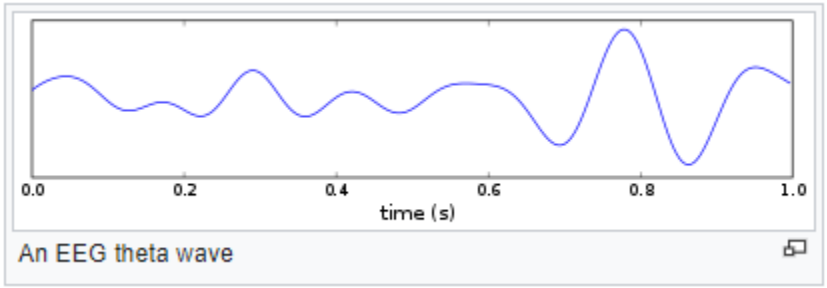
SEIZURE

- 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 abnormalities
- Seizure type
  - Presents as Generalized Tonic-Clonic, myoclonus can occur



An EEG theta wave

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

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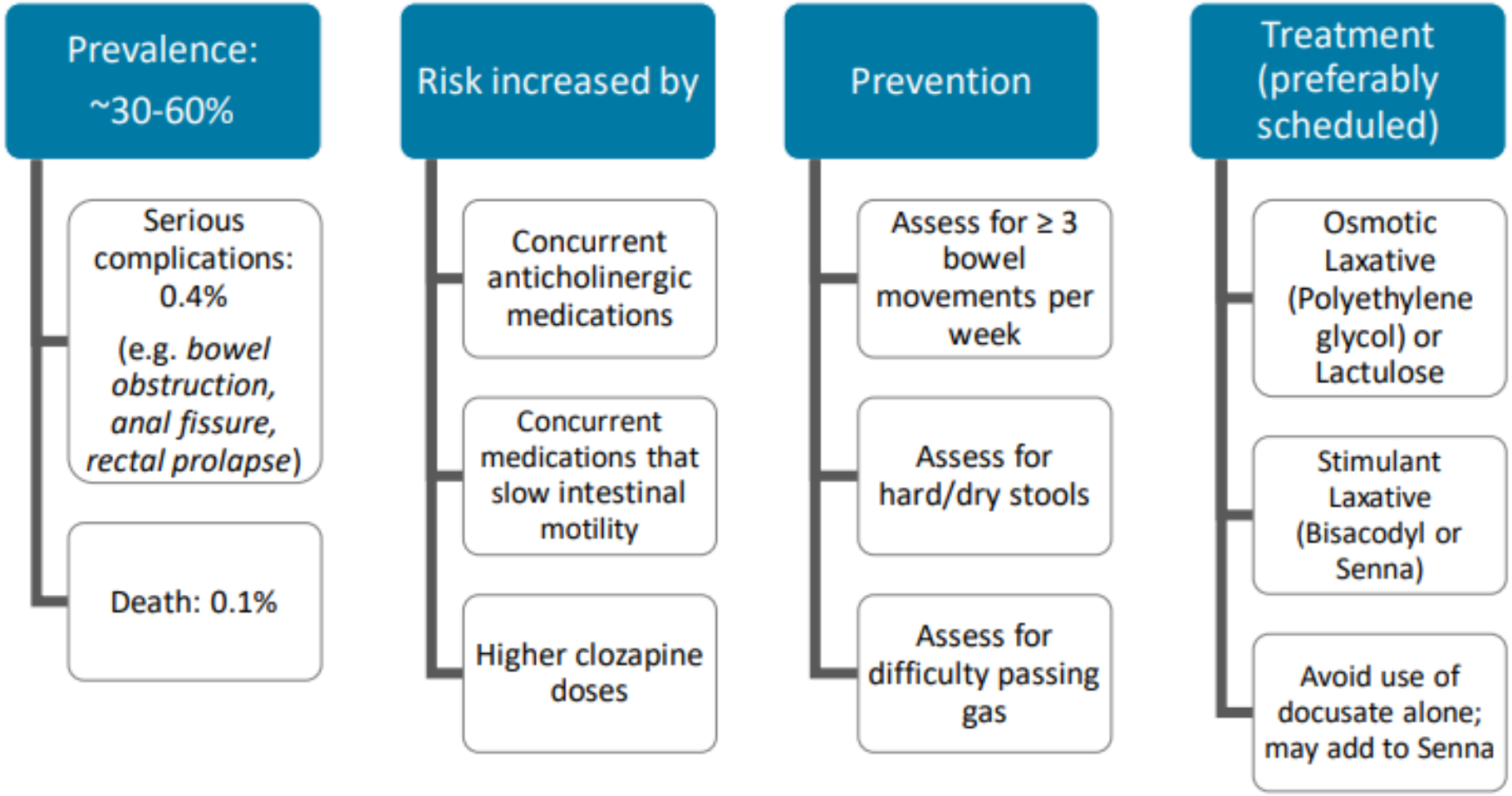
CLOZAPINE OVERVIEW



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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
  - Anticholinergic agents
    - Atropine ophthalmic drops 1%
    - Ipratropium
    - Glycopyrrolate
  - Alpha Blockers
    - Clonidine
    - Terazosin

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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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