SMIAdviser

A Clinical Support System for Serious Mental Illness

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Leveraging Knowledge of Clozapine's Pharmacodynamics and Pharmacokinetics to Improve Outcomes

July 15, 2021

An APA and SAMHSA Initiative

AMERICAN PSYCHIATRIC ASSOCIATION

SAMHSA Substance Abuse and Mental Health Services Administration

CSS-SMI INITIATIVE

The Clinical Support System for Serious Mental Illness (CSS-SMI) is a Substance Abuse and Mental Health Services Administration (SAMHSA) funded initiative implemented by the American Psychiatric Association (APA).

SAMHSA
Substance Abuse and Mental Health Services Administration

AMERICAN PSYCHIATRIC ASSOCIATION

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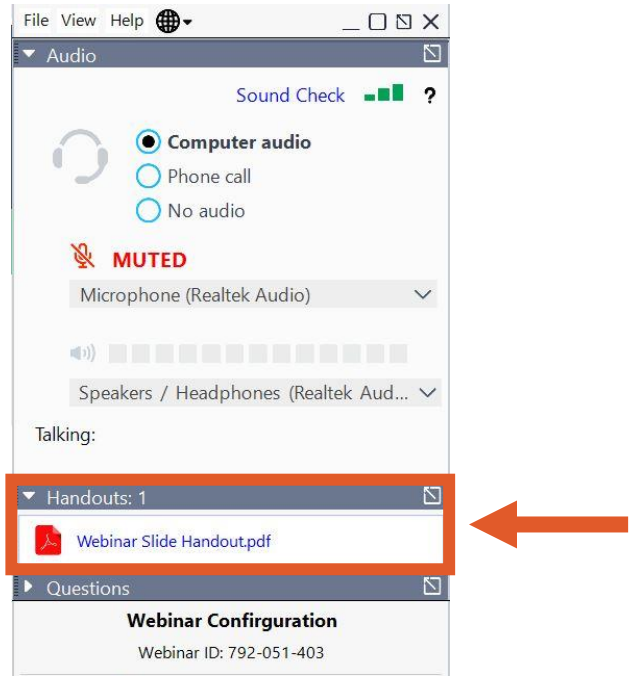

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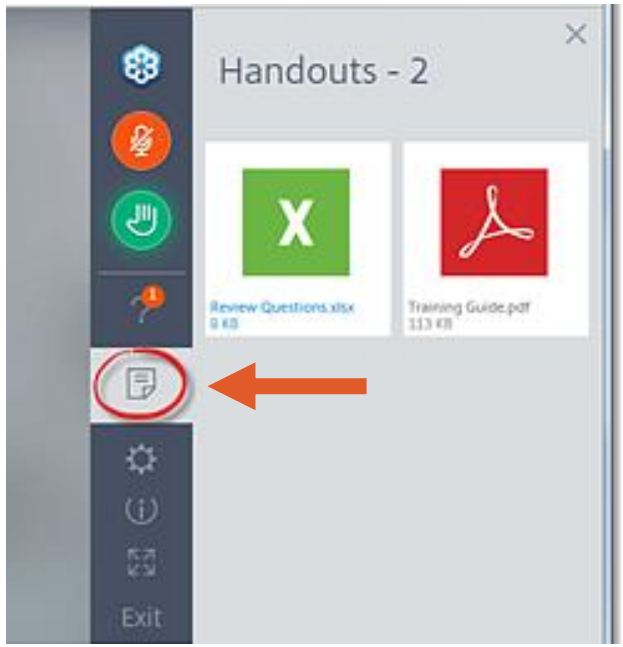

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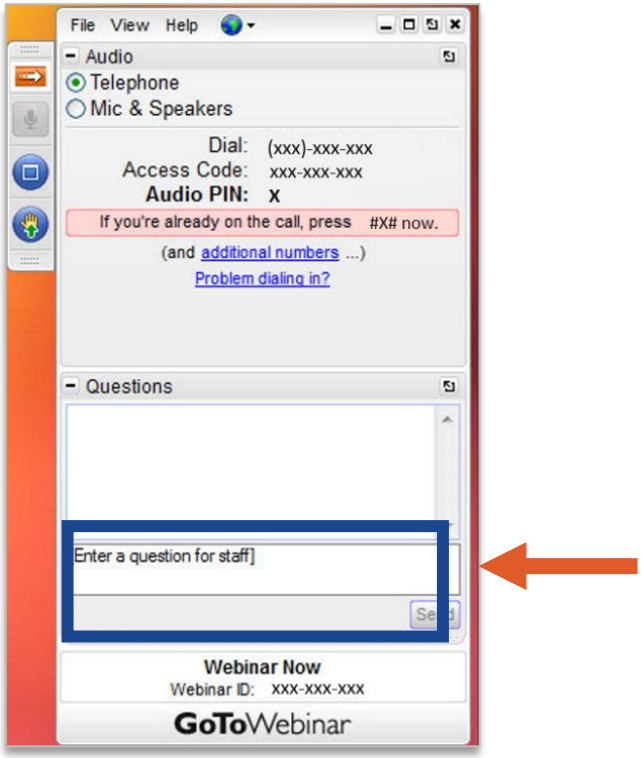

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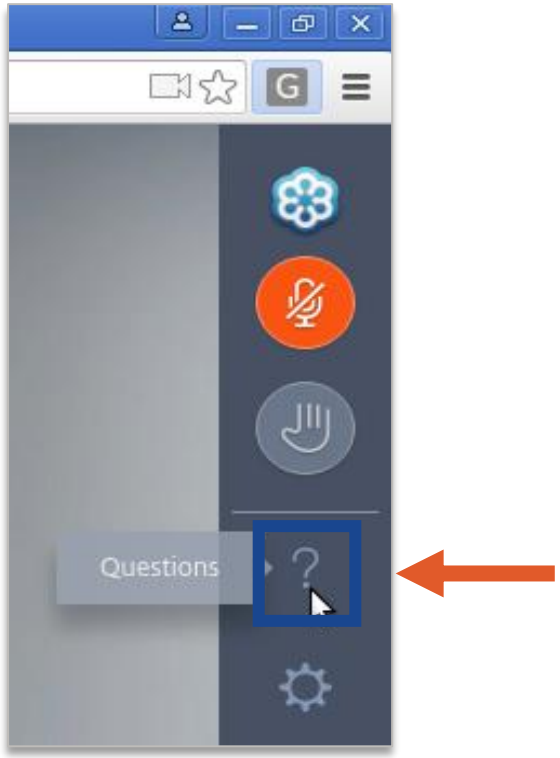


FACULTY

Rob Cotes, MD

Director, Clinical and Research Program for Psychosis
Grady Health System

Associate Professor
Emory University School of Medicine
Department of Psychiatry and Behavioral Sciences

Physician Expert, SMI Adviser

DISCLOSURES

- Rob Cotes has received research funding (to institution) from Otsuka, Lundbeck, Roche, and Alkermes.
- He is a consultant to Saladax Biomedical and the American Psychiatric Association.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to:

- List three common drug-drug interactions with clozapine and if they increase or decrease clozapine levels
- List three scenarios when obtain therapeutic drug monitoring for clozapine as per the ASCP/AGNP guideline
- Calculate clozapine's metabolic ratio and use this information to guide clinical decision making
- List two hypotheses for why clozapine has unique efficacy in treatment resistant schizophrenia

Outline

Optimizing Clozapine Use

- Persistent symptoms of psychosis
- Clozapine pharmacokinetics
- Clozapine pharmacodynamics
- Clozapine side effects

PERSISTENT SYMPTOMS OF PSYCHOSIS

Prevalence

Definition

Effective treatments

Systematic Approach

Treatment Resistant Schizophrenia (TRS)

- Causes considerable suffering, including 34 billion dollars in direct medical costs to the US
- High rate of suicidal ideation (44%)
- High rates of smoking (56%) and substance abuse (51%)
- Likely includes 20-30% of individuals with schizophrenia

Kennedy, J. L., Altar, C. A., Taylor, D. L., Degtiar, I., & Hornberger, J. C. (2014). The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol, 29*(2), 63-76.
Conley, R. R., & Kelly, D. L. (2001). Management of treatment resistance in schizophrenia. *Biol Psychiatry, 50*(11), 898-911.

Prevalence of TRS

- 392 never-treated patients with schizophrenia
- Remission rates at 3 years during follow up treatment
  - 60.3% symptoms
  - 45.4% functioning
  - 57.0% subjective wellbeing
  - 14% never fulfilled any remission criteria

Lambert, M., Naber, D., Schacht, A., Wagner, T., Hundemer, H. P., Karow, A., . . . Schimmelmann, B. G. (2008). Rates and predictors of remission and recovery during 3 years in 392 never-treated patients with schizophrenia. *Acta Psychiatr Scand, 118*(3), 220-229.

Defining TRS

- Highlights of TRIPP Guidelines (minimum requirement)
  - Current symptoms are moderate in severity with at least moderate functional impairment despite:
  - **2 or more antipsychotic medication trials**
  - Antipsychotic dose equivalent to ≥600 mg chlorpromazine per day
  - Antipsychotic trial ≥ 6 weeks at therapeutic dosage
  - ≥80% of prescribed doses taken

Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., . . . Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry, 174*(3), 216-229.

TRS & Clozapine

- Clozapine is the **only** medication approved by the US FDA for TRS
- 4.8% of people with schizophrenia are prescribed clozapine in the US
- Many clinicians do not have clinical competencies necessary to prescribe clozapine, and many organizations do not have supports in place.

Olfson, M., Gerhard, T., Crystal, S., & Stroup, T. S. (2016). Clozapine for Schizophrenia: State Variation in Evidence-Based Practice. *Psychiatr Serv, 67*(2), 152.

When to Use Clozapine – Current APA Guidelines

- Recommends clozapine after “minimal or no response to **two trials** of antipsychotic medication”
- Recommends that patients with schizophrenia be treated with clozapine if the **risk for suicide** attempts or suicide remains substantial despite other treatments.
- Suggests that patients with schizophrenia be treated with clozapine if the risk for **aggressive behavior** remains substantial despite other treatments

American Psychiatric Association. (2020). The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia from https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Clozapine and Suicide

- Schizophrenia lifetime risk of suicide 4.9%
- Clozapine was associated with less suicidal behavior and suicide attempts than olanzapine in the InterSePT study
- In a study combining a Swedish and Finnish registry
  - Clozapine only antipsychotic associated with decreased risk of suicide
  - Clozapine HR 0.64-0.66
  - BZD and Z-drugs associated with increased risk (HR 1.29-1.30, 1.33-1.62, respectively)

- Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry, 62*(3), 247-253. doi:10.1001/archpsyc.62.3.247
- Meltzer, H. Y., Alphs, L., Green, A. I., Altamura, A. C., Anand, R., Bertoldi, A., . . . Potkin, S. (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry, 60*(1), 82-91. doi:10.1001/archpsyc.60.1.82
- Taipale, H., Lähteenvuo, M., Tanskanen, A., Mittendorfer-Rutz, E., & Tiihonen, J. (2020). Comparative Effectiveness of Antipsychotics for Risk of Attempted or Completed Suicide Among Persons With Schizophrenia. *Schizophrenia Bulletin, 47*(1), 23-30. doi:10.1093/schbul/sbaa111

Violence, Schizophrenia, and Clozapine

- Physically assaultive schizophrenia patients randomized to CLO, OLZ, or HAL (N=99)
  - Clozapine superior to OLZ and HAL in reducing assaults
  - For conduct disorder patients specifically (N=53), clozapine was:
    - 4X more likely to result in lower violence than HAL
    - 3X more likely to result in lower violence than OLZ

- Krakowski, M., Tural, U., & Czobor, P. (2021). The Importance of Conduct Disorder in the Treatment of Violence in Schizophrenia: Efficacy of Clozapine Compared With Olanzapine and Haloperidol. *Am J Psychiatry*, appiajp202020010052.

A Systematic Approach to TRS

- 5 C's
  - Correct diagnosis
  - Comorbidities
  - Compliance
  - **Concentration of antipsychotics**
  - Continuous psychosocial stressors

Roerig, J. L. (2019). Clozapine augmentation strategies. *Ment Health Clin, 9*(6), 336-348.

OPTIMIZING CLOZAPINE USE

Pharmacokinetics

Pharmacodynamics

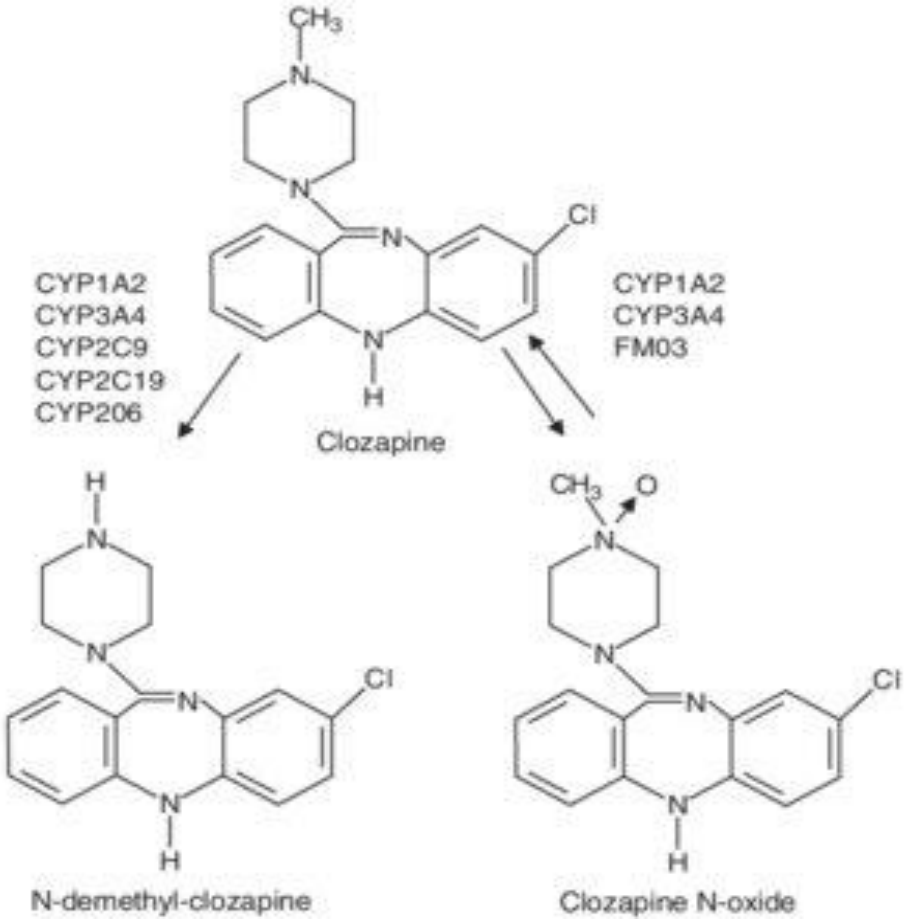
Side Effects

Pharmacokinetics

- **Absorption**
  - Rapidly absorbed through the GI tract
  - Reaches peak plasma concentration within 2 hours
  - Bioavailability of 27-50%, not affected by food
  - Takes 5-7 days to reach steady state
- **Distribution**
  - 97% bound to serum proteins
- **Metabolism and excretion**
  - Undergoes significant first pass metabolism both in gut and liver
  - CYP1A2- main enzyme

Clozapine and metabolites

- Half life
  - Clozapine = 10.5 hours
  - Norclozapine = 19.2 hours
  - Clozapine N-oxide = 8.6 hours



Guitton, C., Kinowski, J.-M., Abbar, M., Chabrand, P. and Bressolle, F. (1999), Clozapine and Metabolite Concentrations during Treatment of Patients with Chronic Schizophrenia. The Journal of Clinical Pharmacology, 39: 721-728. https://doi.org/10.1177/00912709922008245

Clozapine Levels

- AGNP guidelines reference ra
- Risk of ADRs increase at leve

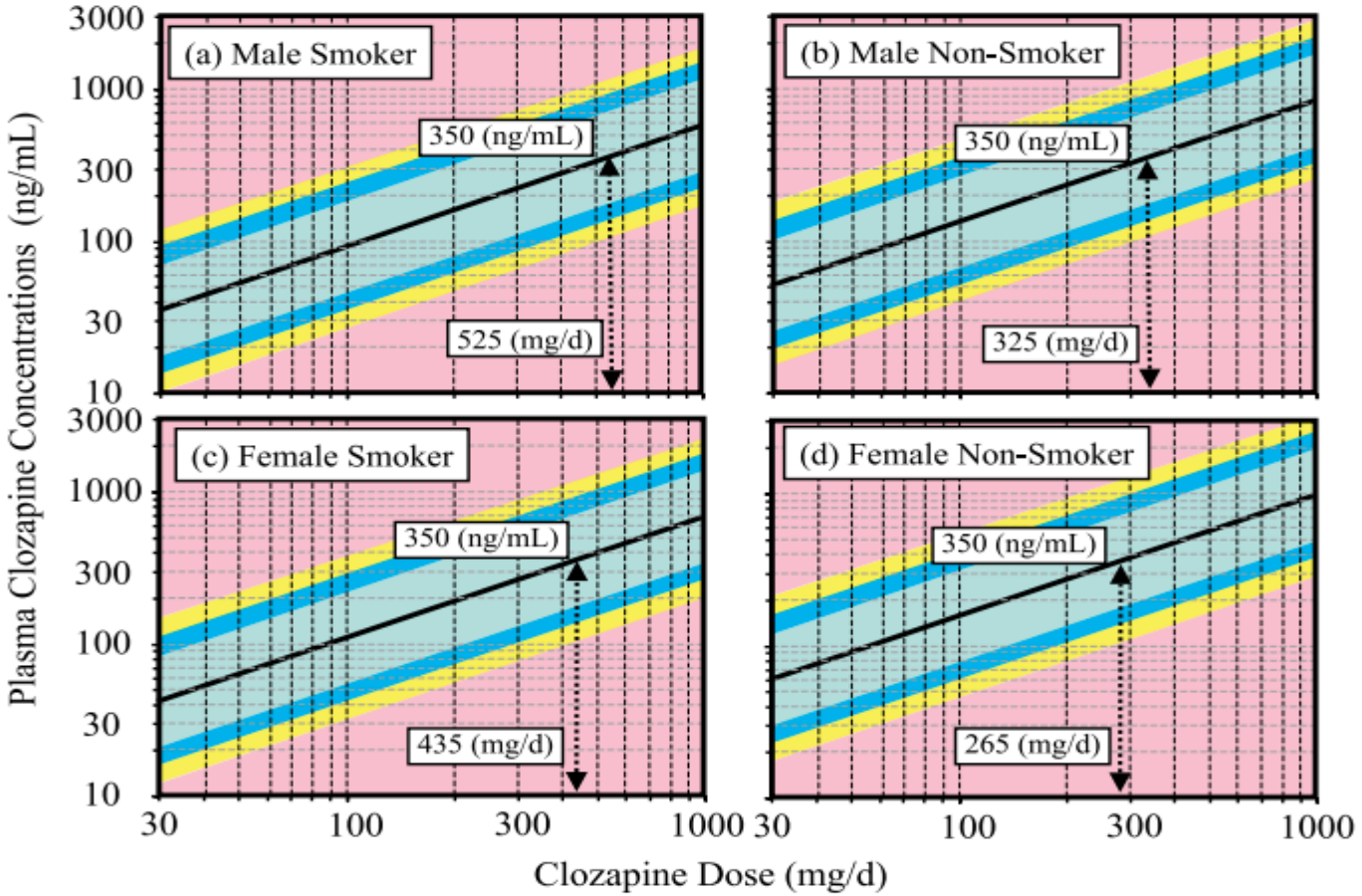
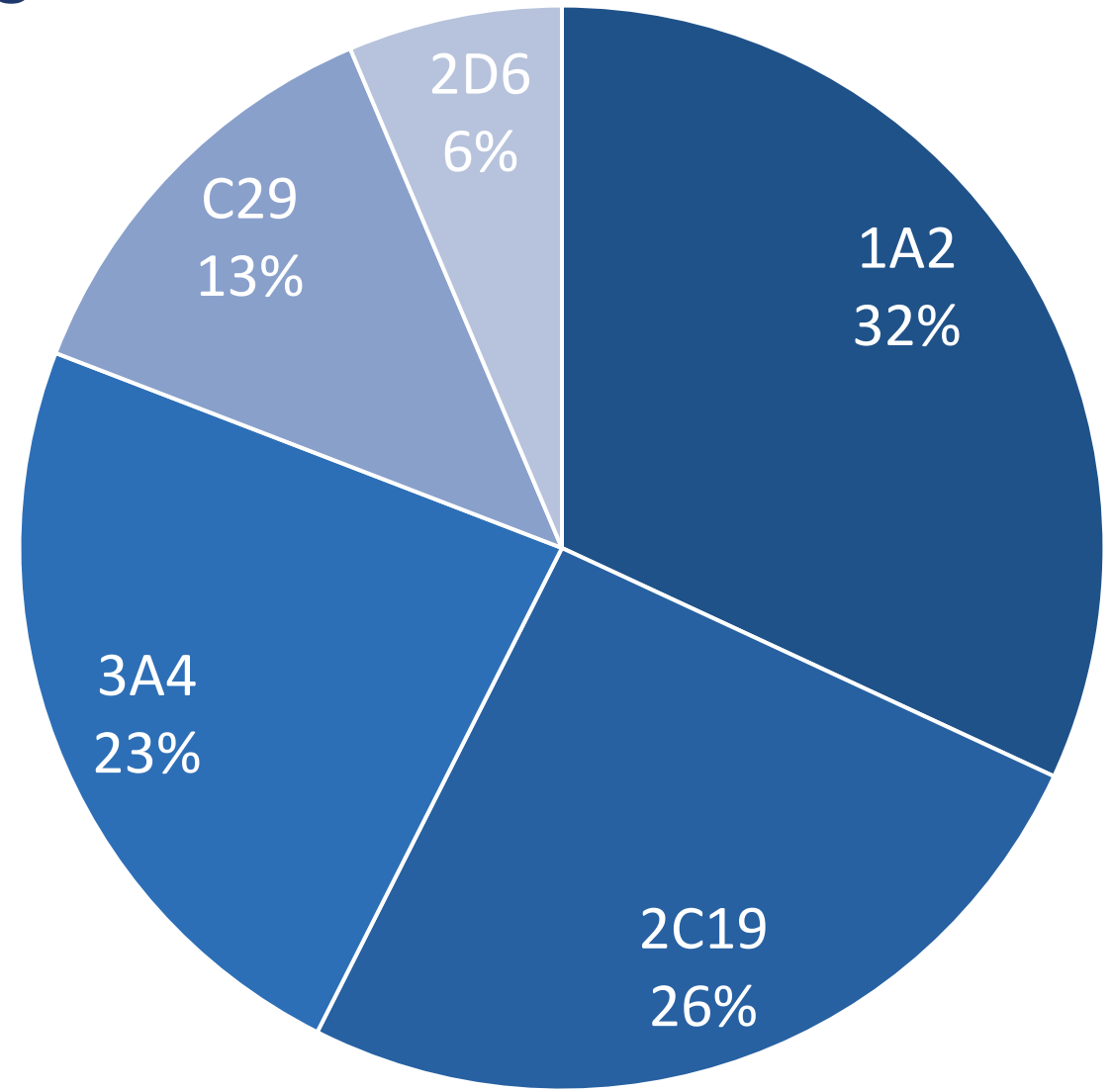


FIGURE 1. Nomograms showing the likelihood of observed plasma clozapine trough concentration for a given daily dose in a 40 year old patient with an average weight of 80 kg (male) or 70 kg (female) and a clozapine/norclozapine MR of 1.32. (a) Male Smoker, (b) Male Nonsmoker, (c) Female Smoker, (d) Female Nonsmoker. The broken arrows show the daily doses that provide the highest likelihood of the plasma clozapine concentration 350 ng/mL. (from this nomogram no likelihood can be estimated for different doses associated with specific clozapine concentrations, ie, the likelihood estimation works only in the vertical direction and not in the horizontal direction).
Key:

- Green area = 50% of patients;
- Green & Blue areas together = 75% of patients;
- Green & Blue & Yellow areas together = 95% of patients;
- Pink area = less than 5% of patients

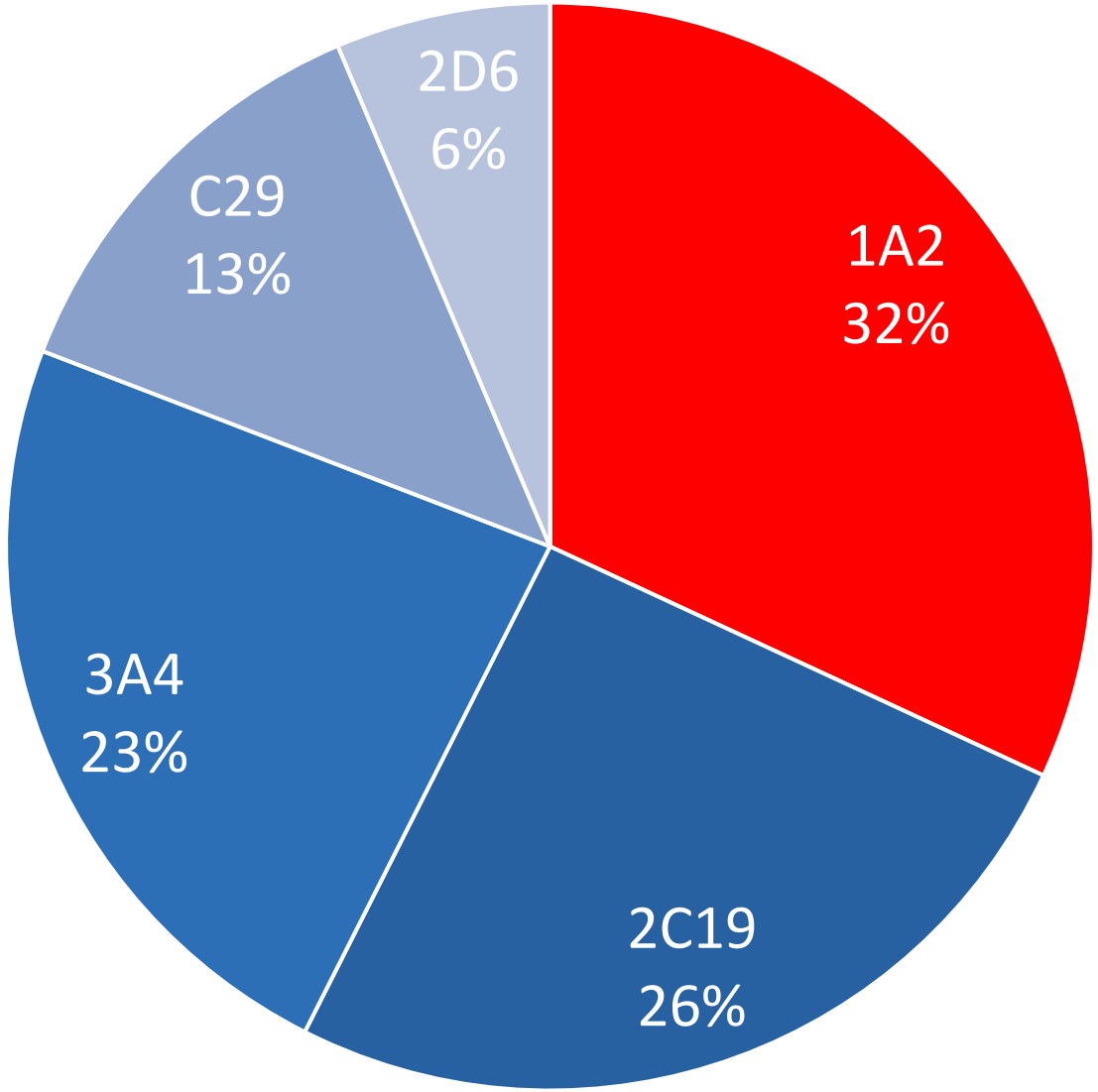
- Rostami-Hodjegan, A., Amin, A. M., Spencer, E. P., Lennard, M. S., Tucker, G. T., & Flanagan, R. J. (2004). Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *J Clin Psychopharmacol, 24*(1), 70-78. doi:10.1097/01.jcp.0000106221.36344.4d

Wheel of Drug-Drug Interactions



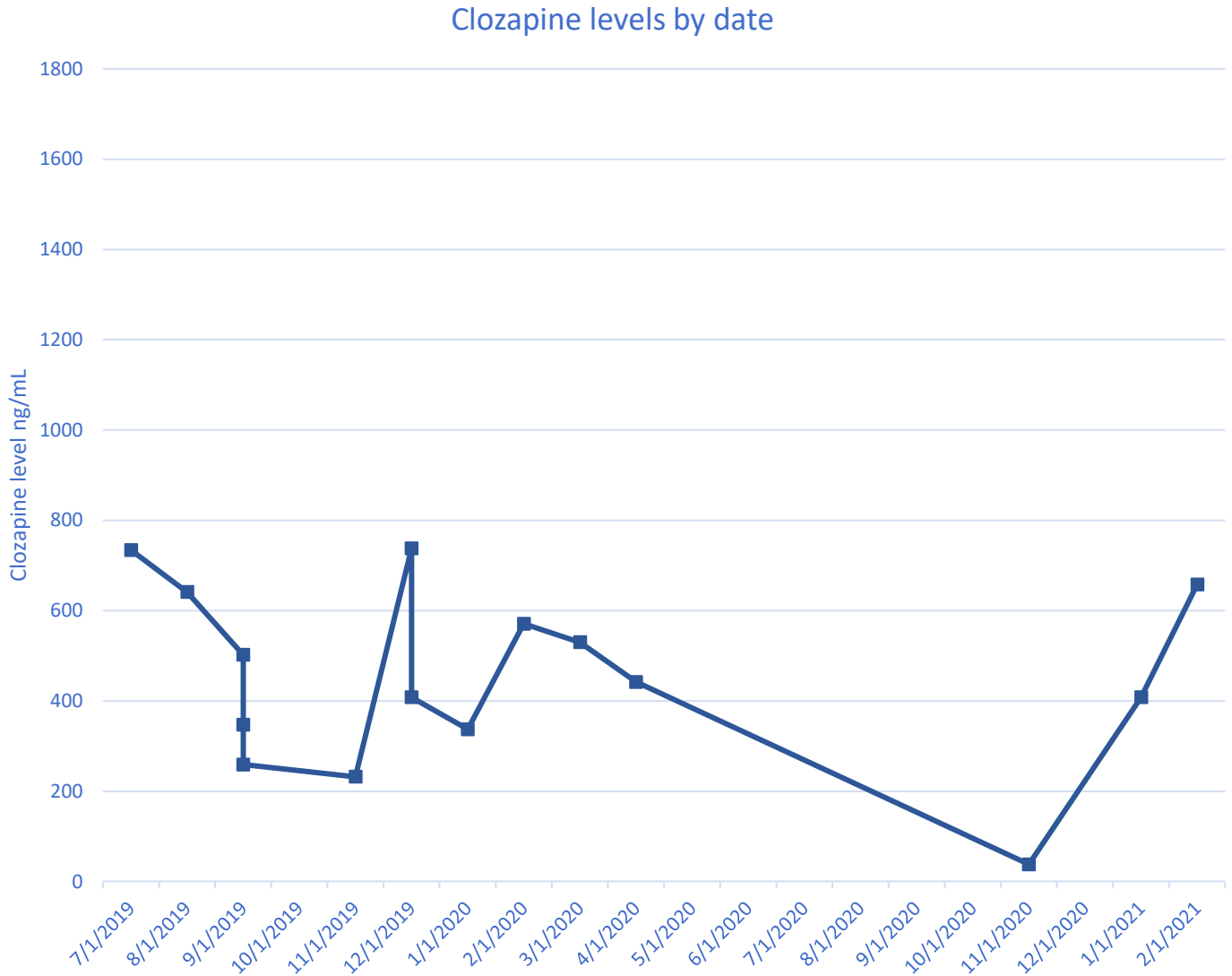
CYP1A2

Inducers Decrease level	Aryl hydrocarbons, broccoli, insulin, modafinil, omeprazole
Inhibitors Increase level	**Ciprofloxacin, fluvoxamine,** verapamil, St. John's wort, cimetidine, caffeine, grapefruit juice



Case example

- 22 y/o male stable on 800 mg of clozapine
- Doing well, in school
- Meets with us in early March to pick up medication and get labs



Case example

- Clozapine level mid-March 1600 ng/mL
- EHR shows seizure at OSH in early March

Unexpectedly high levels (1000 ng/mL)

- Clinically look for
  - Increase in side effects (sialorrhea, tachycardia, sedation)
  - Toxidrome (delirium, slurred speech, sedation)
- Consider EKG
- Consider lab error
- True trough?
- Consider kinetic issues (adding an inhibitor, removal of inducer)
- Reduce dose to get level <1000 ng/mL if adverse effects

Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.

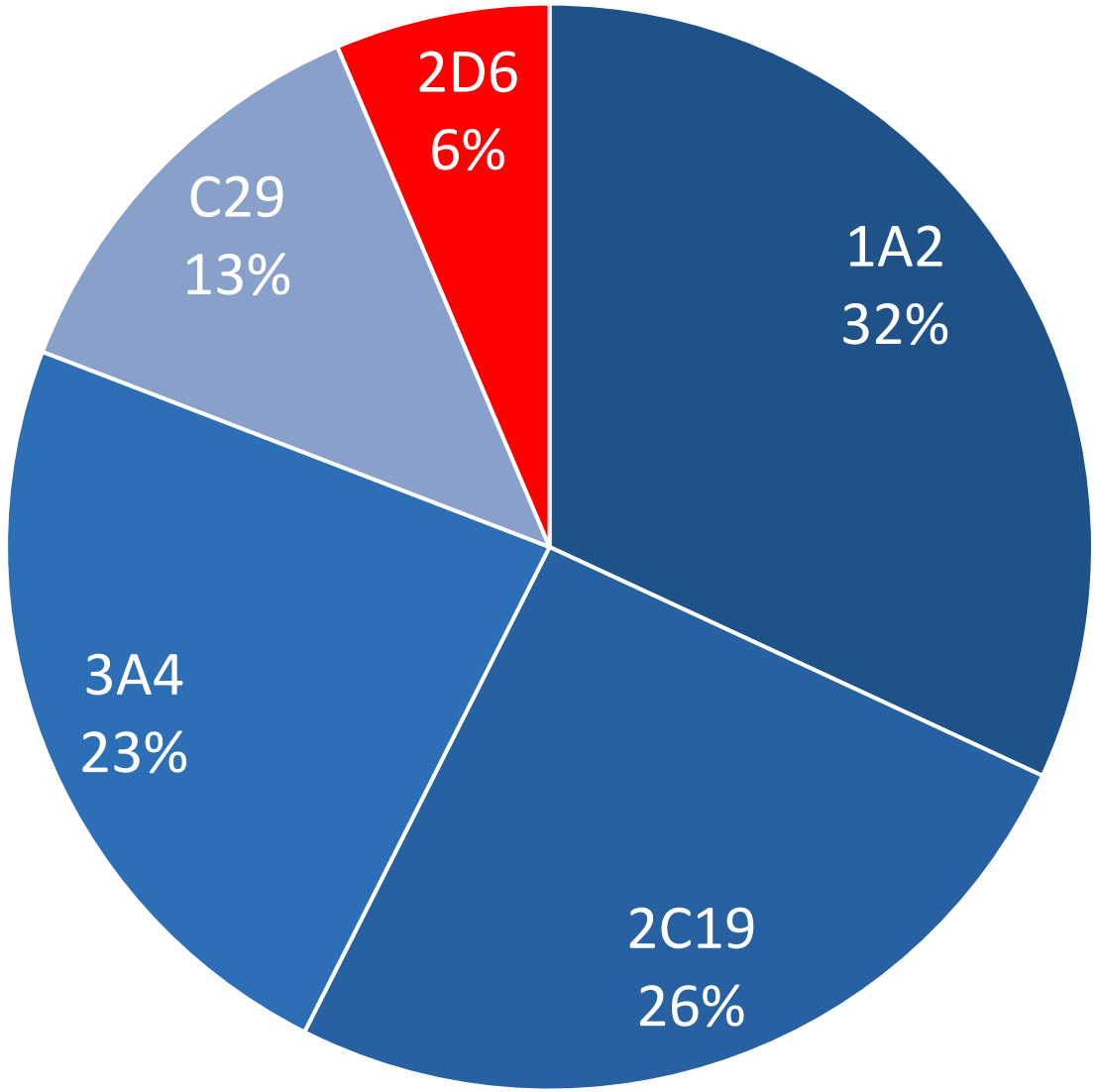
Smoking

- Went from smoking 1 PPD to stopping completely in March 2021
- Aryl hydrocarbons bind to aromatic hydrocarbon receptor -> protein binds to CYP 1A2 promoter region → increase expression of mRNA
- CYP 1A2 is fully induced after regularly smoking 7-12 cigarettes per day
- Can result in 1.7X increase in CYP 1A2 activity
- **Have patients notify you about changes to smoking status**

- Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.

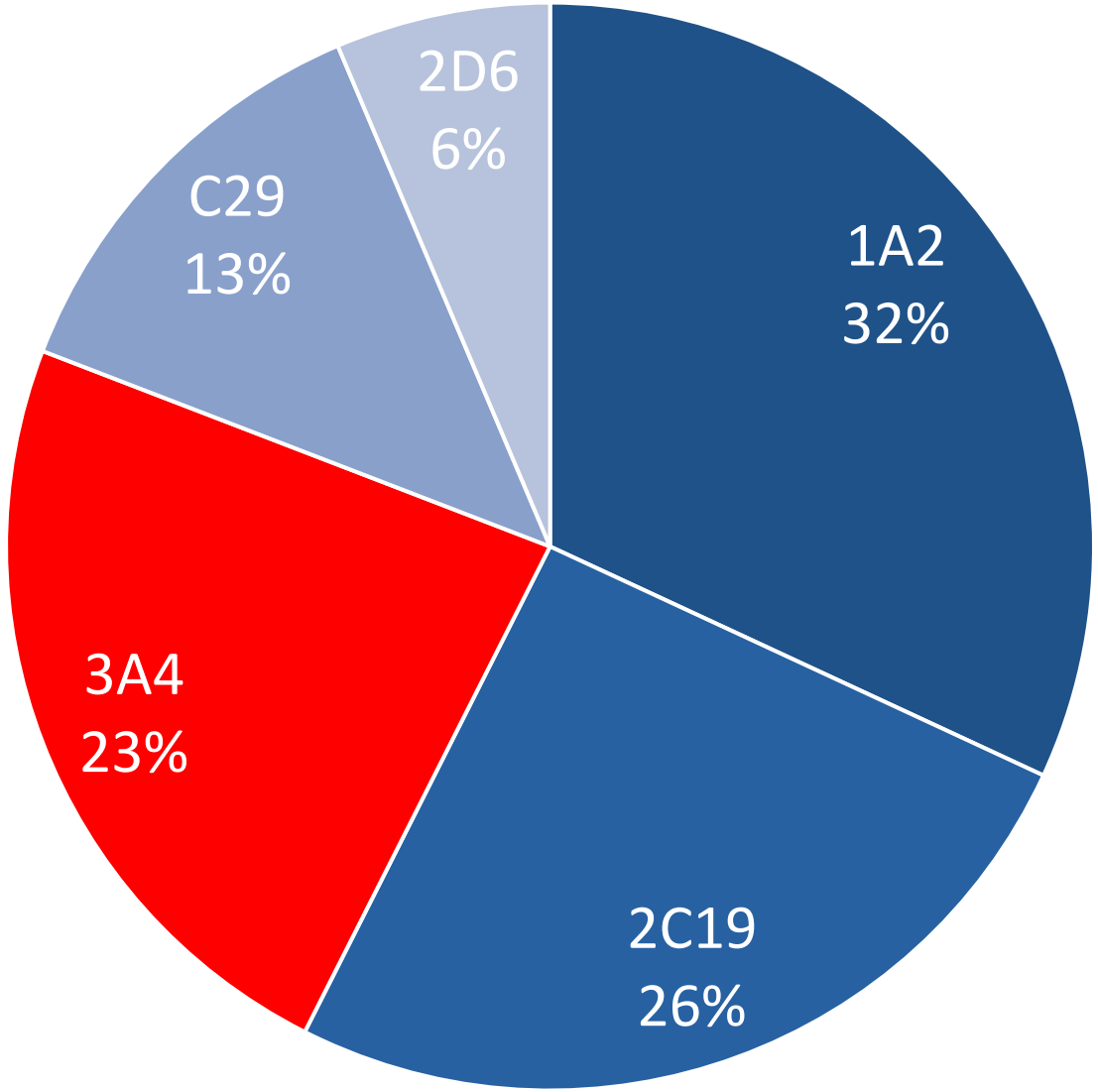
CYP2D6

Inducers Decrease level	Dexamethasone, rifampicin, haloperidol
Inhibitors Increase level	**Fluoxetine, paroxetine, bupropion**, sertraline, terbinafine, buprenorphine, citalopram, escitalopram



CYP3A4

Inducers Decrease level	Phenytoin, carbamazepine, rifampin
Inhibitors Increase level	Ketoconazole, itraconazole, ritonavir, diltiazem, erythromycin, fluconazole



Monitoring Effectiveness

- Consider brief rating scales
- Symptom relief
  - Positive symptoms decreased: disorganization, hallucinations, delusions
- Clozapine blood levels
  - Levels useful for adherence, more side-effects, possibly efficacy, drug-drug interactions
  - Trough: 12 hours after the last dose (or right before AM dose)

Schulte P (2003) What is an adequate trial with clozapine? Therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. Clinical Pharmacokinetics 42: 607–618
Williams, A. M., & Park, S. H. (2015). Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs, 29*(2), 101-111.

Antipsychotics for which TDM is “strongly recommended”

- **Clozapine**
- Fluphenazine
- Haloperidol
- Olanzapine
- Perazine
- Perphenzaine

Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, Robinson DG, Goff DC, Kelly DL, Freudenreich O, Piacentino D, Paulzen M, Conca A, Zernig G, Haen E, Baumann P, Hiemke C, Gründer G; American Society of Clinical Psychopharmacology, Pharmakopsychiatrie TTDMTFOTAFNU. Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. doi: 10.4088/JCP.19cs13169. PMID: 32433836.

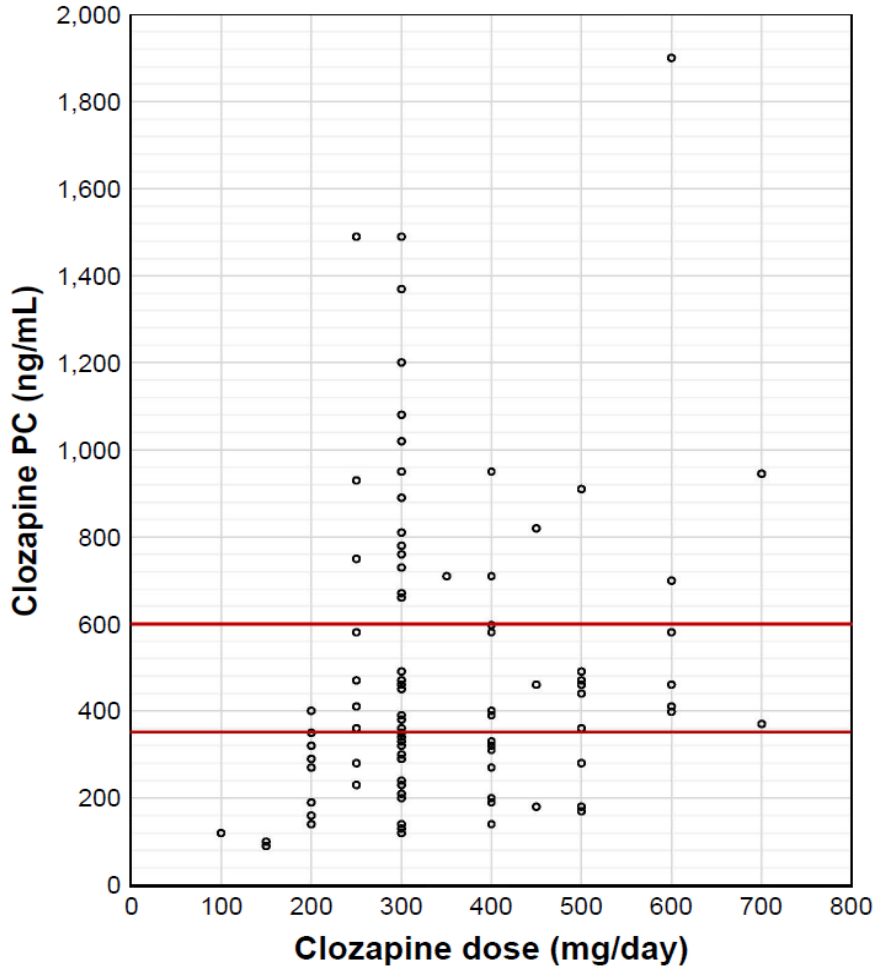
ASCP/AGNP TDM may be valuable in the following situations:

- Uncertain adherence
- Lack of response within established dose ranges
- Symptom recurrence during maintenance tx
- Adverse drug reactions
- Combination tx with inducers or inhibitors
- Certain ancestral heritage
- High or low body weight
- Special populations (pregnant, children, elderly)
- Pts with intellectual disability
- Forensic patients
- Hepatic or renal dysfunction
- Acute of chronic inflammatory conditions
- Post-operative care for restrictive GI resection
- Switching from original preparations to generics
- Switching from between oral to LAI agents

Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, Robinson DG, Goff DC, Kelly DL, Freudenreich O, Piacentino D, Paulzen M, Conca A, Zernig G, Haen E, Baumann P, Hiemke C, Gründer G; American Society of Clinical Psychopharmacology, Pharmakopsychiatrie TTDMTFOTAFNU. Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. doi: 10.4088/JCP.19cs13169. PMID: 32433836.

Must check to know

- How many patients using clozapine in common clinical practice have clozapine plasma concentration (PC) levels in the proposed reference range?
- Only 33% of patients were within reference range of 350-600 ng/mL



Mayerova, M., Ustohal, L., Jarkovsky, J., Pivnicka, J., Kasparek, T., & Ceskova, E. (2018). Influence of dose, gender, and cigarette smoking on clozapine plasma concentrations. *Neuropsychiatric disease and treatment, 14*, 1535-1543. doi:10.2147/NDT.S163839

Metabolic Ratio

- Metabolic Ratio = clozapine / norclozapine level
- Significant changes help to understand presence of an inhibitor or inducer
- Expected MR
  - Non-smoking male = 1.32 (extensive metabolizers at all CYP isoenzymes)
- Remains unchanged during periods of poor adherence UNLESS clozapine is taken just prior to the level

Interpreting MR ratio

Expected value
for nonsmokers

<1.0 | 1.3 | >1.7 | >3.0

+ Inducer (smoking, carbamazepine, omeprazole)

OR

CYP 1A2 ultra-rapid metabolizer

+ Inhibitor (Fluoxetine, paroxetine, bupropion, etc)

OR

CYP 1A2 or CYP 2D6 poor metabolizers

++ Inhibitor (ciprofloxacin, fluvoxamine)

OR

Viral or bacterial illness

Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.

Optimizing patient outcomes using clozapine TDM

- Stakes are high in people taking clozapine, no other medication would be expected to work for TRS
- 5 to 7 day delay in clozapine level makes real-time decision-making challenging, but helps provide clues in retrospect
- Can help determine if clozapine is within the therapeutic range
  - If too high: dose reduction can reduce tolerability issues, improve adherence, can help identify point of futility (1000 ng/mL), can point to kinetic issues
  - If too low: dose increase can improve efficacy, can point to kinetic issues

So practically, when do we get clozapine levels?

- **Low threshold**
- Early in the titration – at least at 100 mg
- Any dose increase
- Suspicion for nonadherence
- New adverse effects
- Lack of response

PSTAR

Persistent Symptoms: Treatment, Assessment and Recovery

OPTIMIZING CLOZAPINE USE

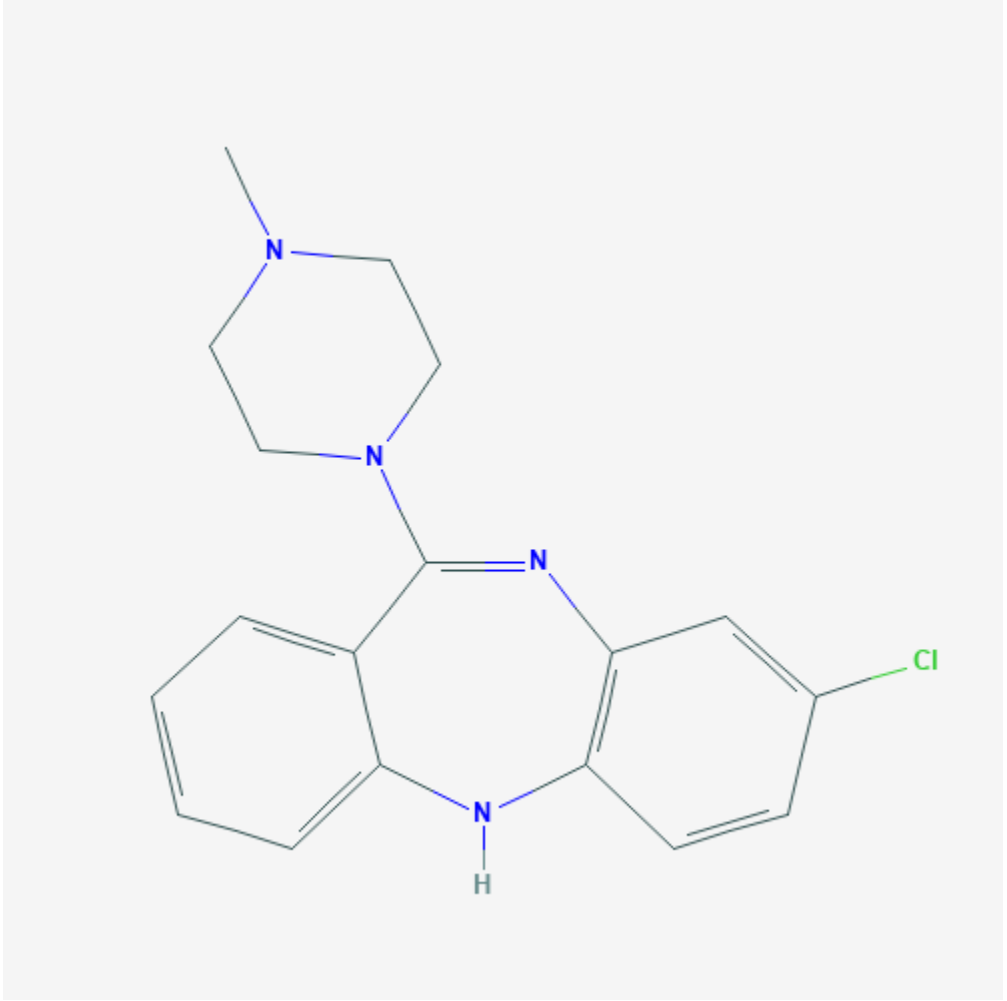
Pharmacokinetics

Pharmacodynamics

Side Effects

Pharmacodynamics

- Incompletely understood
- Likely most complex profile of any antipsychotic
- **Antagonist** at D2, H1, alpha1, M1, M3
- **Inverse agonist** at 5HT2A
- **Partial agonist** at 5HT1A



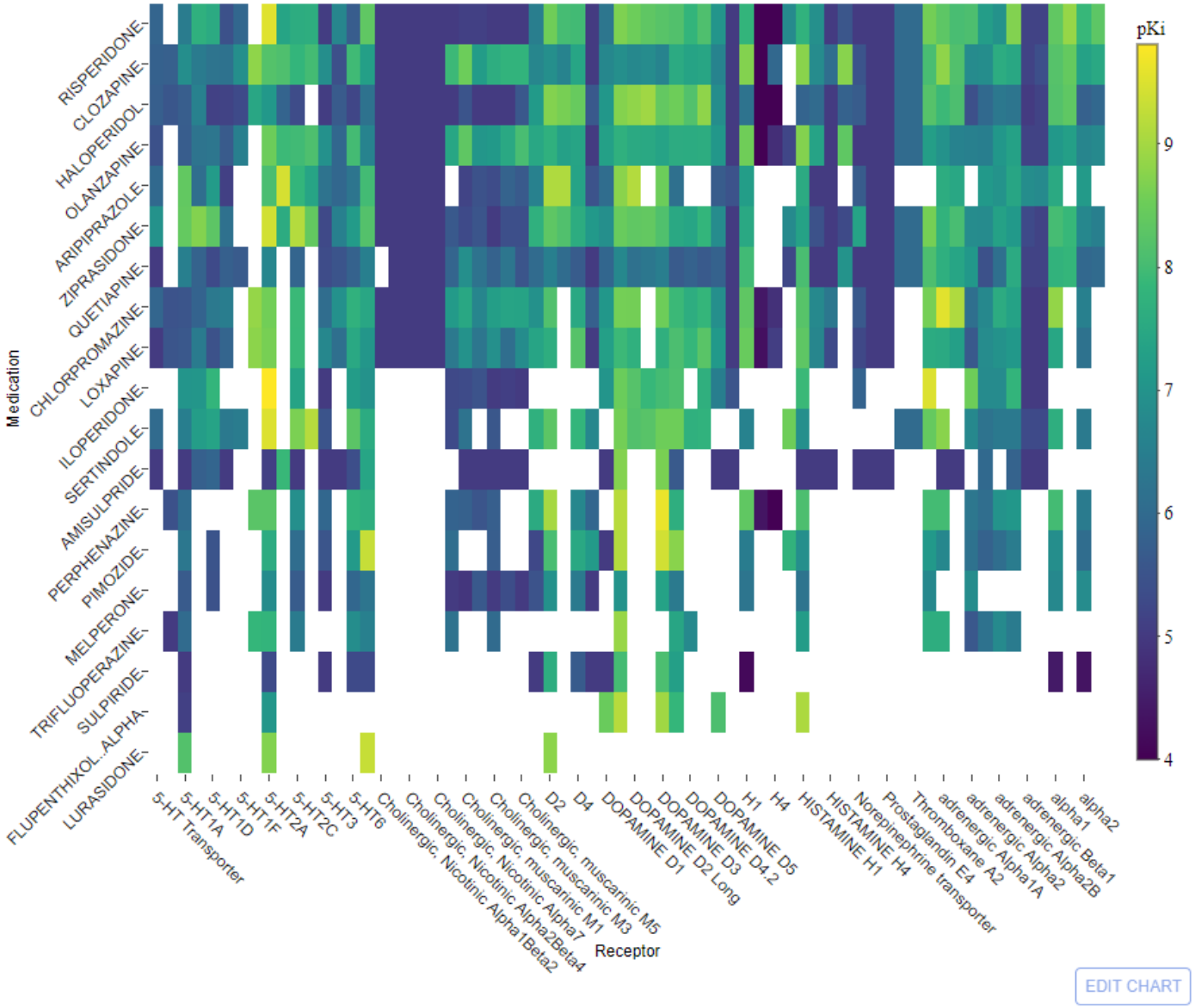
Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.
Image from: https://pubchem.ncbi.nlm.nih.gov/compound/135398737#section=2D-Structure

Inhibitory Constant (*Ki*)

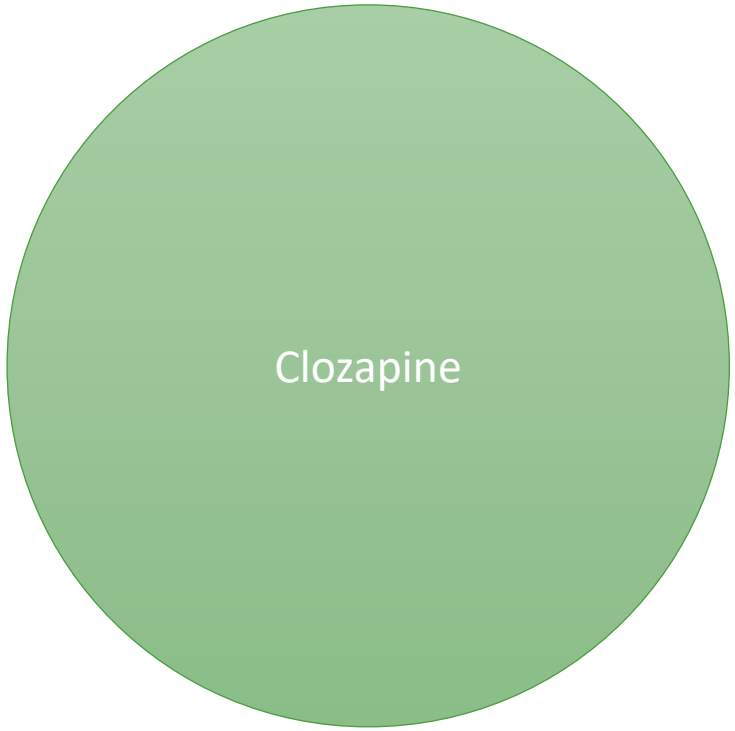
- Measures potency of an inhibitor
- *Ki* = Concentration which 50% of the receptor is occupied
- **Lower *Ki* means higher affinity**
- Key resources:
  - PDSP Ki database (pdsp.unc.edu/databases)
- 718 results for human cloned receptors for clozapine as of 4/14/21

Receptor Binding

- Using data from PDSP
- https://www.danwjoyce.com/blog/2018/6/7/visualising-pharmacology-part-one
- This resource measured in *pKi* = -log10(*Ki*) where 9 means higher affinity



Pharmacodynamics - Efficacy

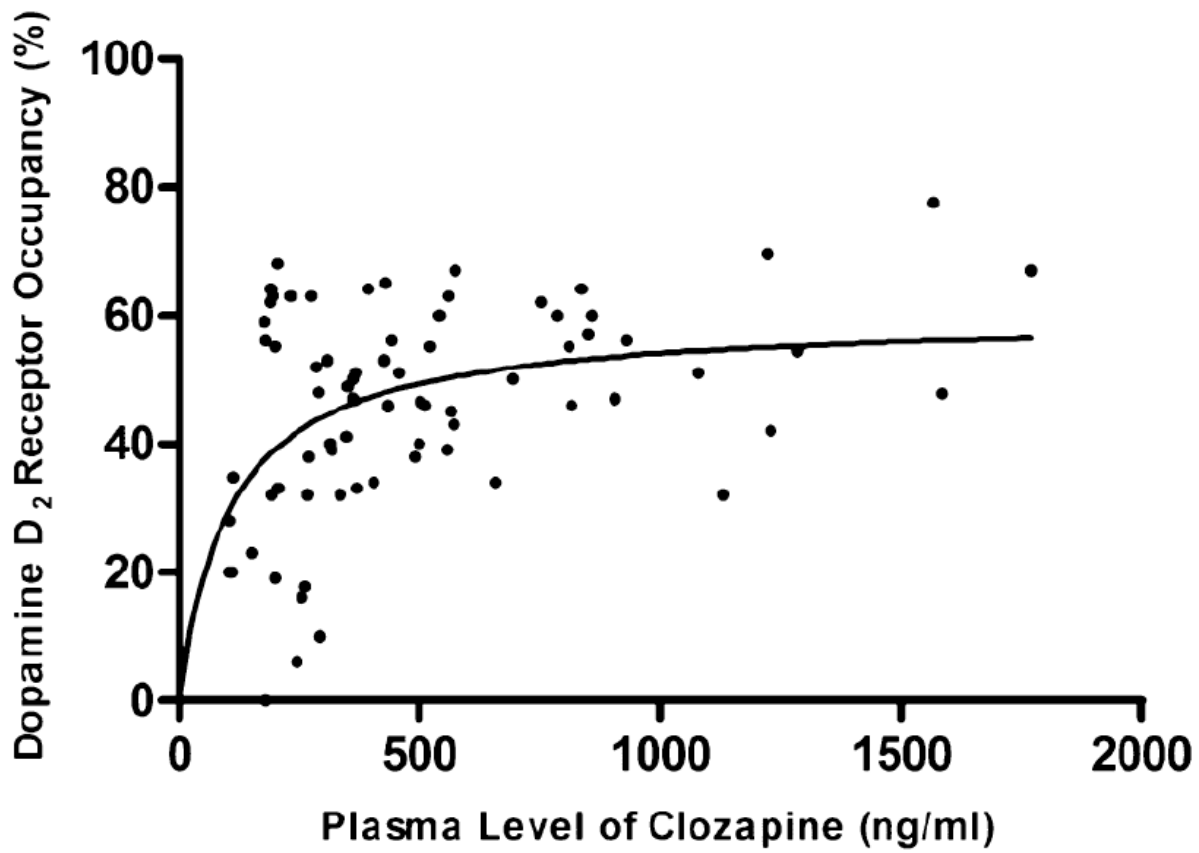


Drug	D2	5HT2A	D2/5HT2A	D4
Clozapine	210	3	81	23
Haloperidol	3	61	0.04	4
Risperidone	4	0.1	38	7
Olanzapine	20	2	13	17
Quetiapine	770	31	25	>1000

Solmi, M., Murru, A., Pacchiarotti, I., Undurraga, J., Veronese, N., Fornaro, M., . . . Carvalho, A. F. (2017). Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag, 13*, 757-777. doi:10.2147/TCRM.S117321

Richtand, N. M., Welge, J. A., Logue, A. D., Keck, P. E., Jr., Strakowski, S. M., & McNamara, R. K. (2007). Dopamine and serotonin receptor binding and antipsychotic efficacy. *Neuropsychopharmacology, 32*(8), 1715-1726. doi:10.1038/sj.npp.1301305

Clozapine D2 Occupancy by Plasma Level



- In contrast, risperidone, olanzapine, and haloperidol occupy D2 80% at therapeutic levels
- Clozapine also is “fast-off” D2 (15s) versus haloperidol (38 min), risperidone (27 min)

Uchida et al. Predicting dopamine D2 receptor occupancy plasma levels of antipsychotic drugs: a systematic review and pooled analysis. J Clin Psychopmarmacol 2011; 31: 318-25; Seeman, P. (2006). Targeting the dopamine D2 receptor in schizophrenia. *Expert Opinion on Therapeutic Targets, 10*(4), 515-531. doi:10.1517/14728222.10.4.515

Unique (and Enigmatic) Mechanism of Action

Hypothesis	Evidence in Favor	Evidence Against
Dopamine D2 receptor	Low D2 receptor occupancy Rapid D2 receptor dissociation	Quetiapine also has low D2 receptor occupancy and rapid D2 receptor dissociation
Dopamine D4 receptor	High D4 receptor affinity High D4/D2 receptor affinity ratio	Olanzapine (high D4 receptor affinity), ziprasidone (high D4 receptor affinity), asenapine (high D4/D2 affinity ratio), pure D4 receptor antagonists ineffective
Serotonin receptors	High 5HT2A/D2 receptor affinity ratio	True of most atypicals, pure 5HT-2A receptor antagonists ineffective

Adapted from: Nucifora FC, Jr., Mihaljevic M, Lee BJ, et al: Clozapine as a Model for Antipsychotic Development. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 2017; 14:750-761

OPTIMIZING CLOZAPINE USE

Pharmacokinetics

Pharmacodynamics

Side Effects

Neutropenia

- Mechanism: unclear, possibly-immune mediated rather than direct bone marrow toxicity
- ANC weekly first 6 mo, q2 weeks mo 6-12, monthly at 12 months
- 3.8% neutropenia
- 0.9% severe neutropenia
- 0.013% death due to neutropenia (1/7700)
- Peak incidence 1 month after initiation
- 89% cases severe neutropenia occurred at 1 year

- Myles, N., Myles, H., Xia, S., Large, M., Kisely, S., Galletly, C., . . . Siskind, D. (2018). Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand, 138*(2), 101-109. doi:10.1111/acps.12898

47

Myocarditis

- Mechanism: unclear, IgE hypersensitivity reaction, increased cytokines release
- Incidence varies, largest meta-analysis 0.7%
- Mean time until onset 17 days, 82% occurring between days 14-21
- Known associations: sodium valproate, age, rapid clozapine titrations
- Non-specific symptoms: fever, fatigue, flu-like symptoms, chest pain, tachycardia, palpitations, hypotension, dyspnea, signs of heart failure, electrocardiographic changes
- Screening protocol: weekly CRP, troponin I/T for first 4-6 weeks
- Management: discontinue clozapine and obtain cardiac evaluation (EKG, TTE, cardiac MRI). Have been successful rechallenges.

Siskind, D., Sidhu, A., Cross, J., Chua, Y. T., Myles, N., Cohen, D., & Kisely, S. (2020). Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Aust N Z J Psychiatry, 54*(5), 467-481. doi:10.1177/0004867419898760. Ronaldson, K. J., Fitzgerald, P. B., Taylor, A. J., Topliss, D. J., & McNeil, J. J. (2011). A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry, 45*(6), 458-465. Ronaldson, K. J., Fitzgerald, P. B., Taylor, A. J., Topliss, D. J., Wolfe, R., & McNeil, J. J. (2012). Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res, 141*(2-3), 173-178. Cook, S. C., Ferguson, B. A., Cotes, R. O., Heinrich, T. W., & Schwartz, A. C. (2015). Clozapine-Induced Myocarditis: Prevention and Considerations in Rechallenge. *Psychosomatics, 56*(6), 685-690.

Seizures

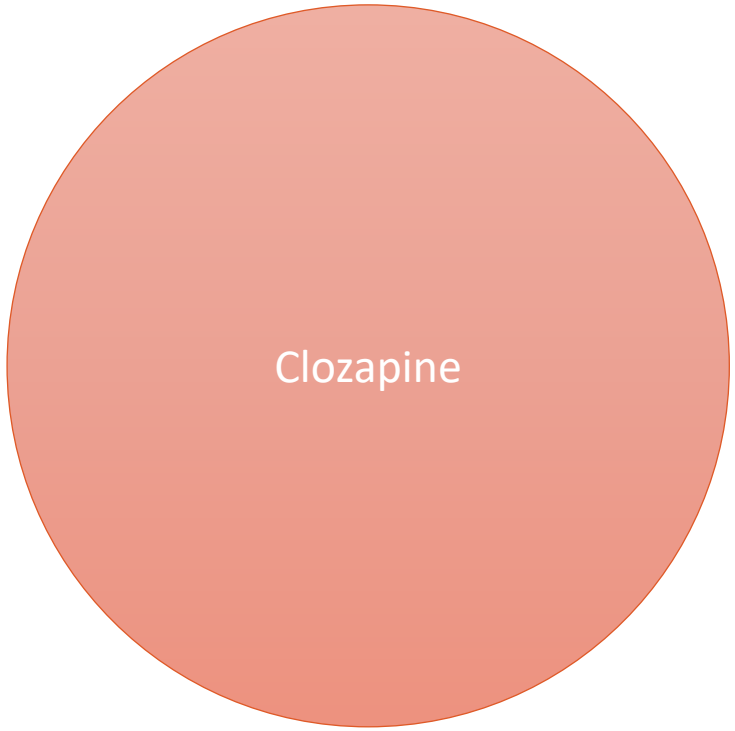
- Mechanism: unclear, possible selectivity of binding at D2 mesolimbic receptors
- 61/1742 (3.5%) in Phase II-III Clinical Trials
- Adjusted hazard ratio of 3 compared to other antipsychotics
- Often occurs during dose increase or CYP1A2 inhibitor
- Unclear if dose dependent, but levels >1000 ng/mL may be a RF
- Management: seizures can usually be controlled with dosage reduction or adding an antiepileptic medication such as valproate

Pacia, S. V., & Devinsky, O. (1994). Clozapine-related seizures: experience with 5,629 patients. *Neurology, 44*(12), 2247-2249.
Williams, A. M., & Park, S. H. (2015). Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs, 29*(2), 101-111.
Wu, C. S., Wang, S. C., Yeh, I. J., & Liu, S. K. (2016). Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. *J Clin Psychiatry, 77*(5), e573-579
Alper, K., Schwartz, K. A., Kolts, R. L., & Khan, A. (2007). Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports. *Biological Psychiatry, 62*(4), 345-354. doi:https://doi.org/10.1016/j.biopsych.2006.09.023

Understanding pharmacodynamic properties to predict other side effects

- Sedation
- Tachycardia
- Orthostatic hypotension
- Constipation
- Hyperphagia/weight gain
- Sialorrhea

Sedation



Drug	α1	H1	M2
Clozapine	7	3	204
Haloperidol	17	260	>10,000
Risperidone	3	5	>10,000
Olanzapine	44	0.1	622

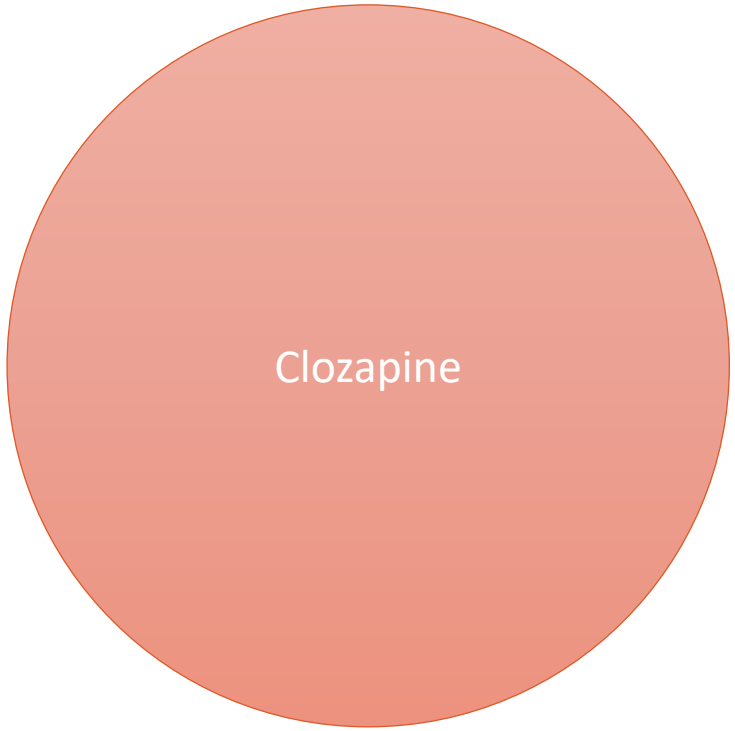
Solmi, M., Murru, A., Pacchiarotti, I., Undurraga, J., Veronese, N., Fornaro, M., . . . Carvalho, A. F. (2017). Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag, 13*, 757-777. doi:10.2147/TCRM.S117321

Sedation

- This occurs in most patients as they titrate the dosage up
- After a patient is improving clinically, typically at 200 or 300 mg per day, the full dosage is often moved to bedtime, moving sedation to nighttime. With this, people may sleep longer than usual, or have morning drowsiness.
- Sedation decreases over time
  - patients should not drive or engage in potentially dangerous activities while starting clozapine until it is clear that sedation is no longer an issue.
  - if sedation is greater than expected, the possibility of drug-drug interactions should be considered, and a clozapine plasma level can be helpful
- Morning drowsiness can be helped by caffeine and being active

Takeuchi, H., Powell, V., Geisler, S., DeSanti, M., Fervaha, G., Agid, O., . . . Remington, G. (2016). Clozapine administration in clinical practice: once-daily versus divided dosing. *Acta Psychiatr Scand, 134*(3), 234-240.

Tachycardia



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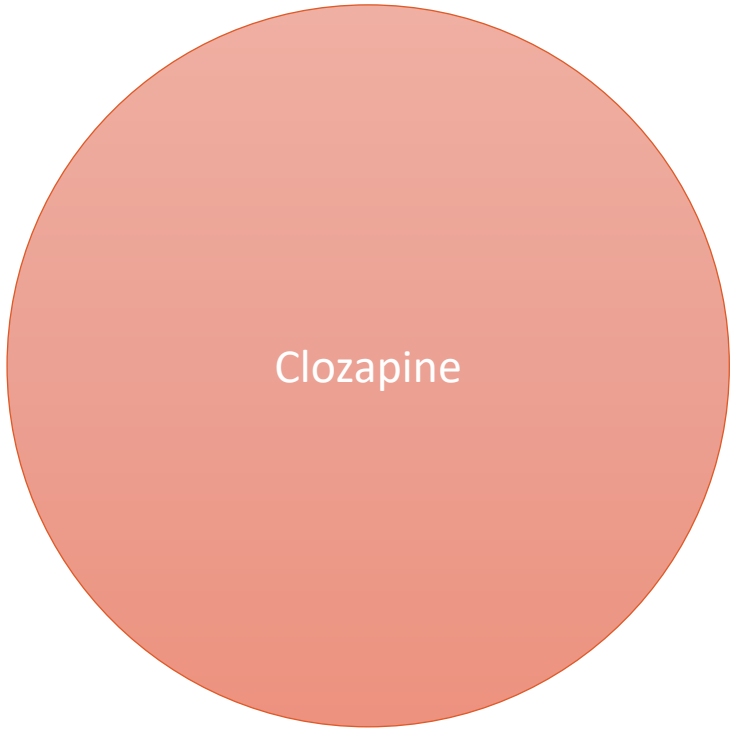
Tachycardia

- Tachycardia is heart rate above 100 BPM, and can be a side effect
  - up to 25% of people taking clozapine experience tachycardia
- Evaluation of tachycardia can include an EKG, and excludes other causes: fever, shortness of breath, smoking, caffeine, simulants, hyperthyroidism, cardiovascular disorders, orthostatic hypotension, other medications
- Heart rate up to 120 beats per minute is often asymptomatic
  - can improve over time; is typically not treated
- Symptomatic tachycardia or > 120 BPM should lead to additional evaluation, intervention or referral
- Management
  - reduce smoking, caffeine, stimulant medications, stimulating supplements
  - Beta-blockers have been used, however they can cause side effects, such as orthostatic hypotension

Zhang, D., Wang, W., & Li, F. (2016). Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. *Cmaj, 188*(15), E384-e392.

Orthostatic hypotension



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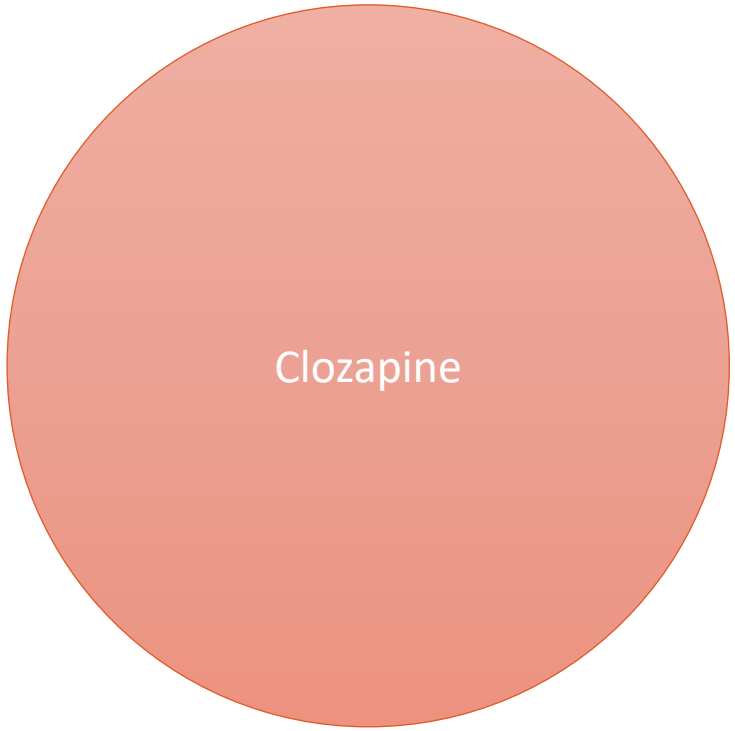
Orthostatic hypotension

- Definition: drop in blood pressure when changing from lying or sitting to standing; can lead to falls upon standing
- Risk is highest during early clozapine titration, and with rapid dose increases
- Management
  - sit on the edge of the bed for a minute before standing up, otherwise move slowly from lying or sitting to standing.
  - divide the clozapine dose during the day, and slow dose titration
  - increase fluid and salt intake
  - fludrocortisone

Testani, M., Jr. (1994). Clozapine-induced orthostatic hypotension treated with fludrocortisone. *J Clin Psychiatry, 55*(11), 497-498.

Constipation



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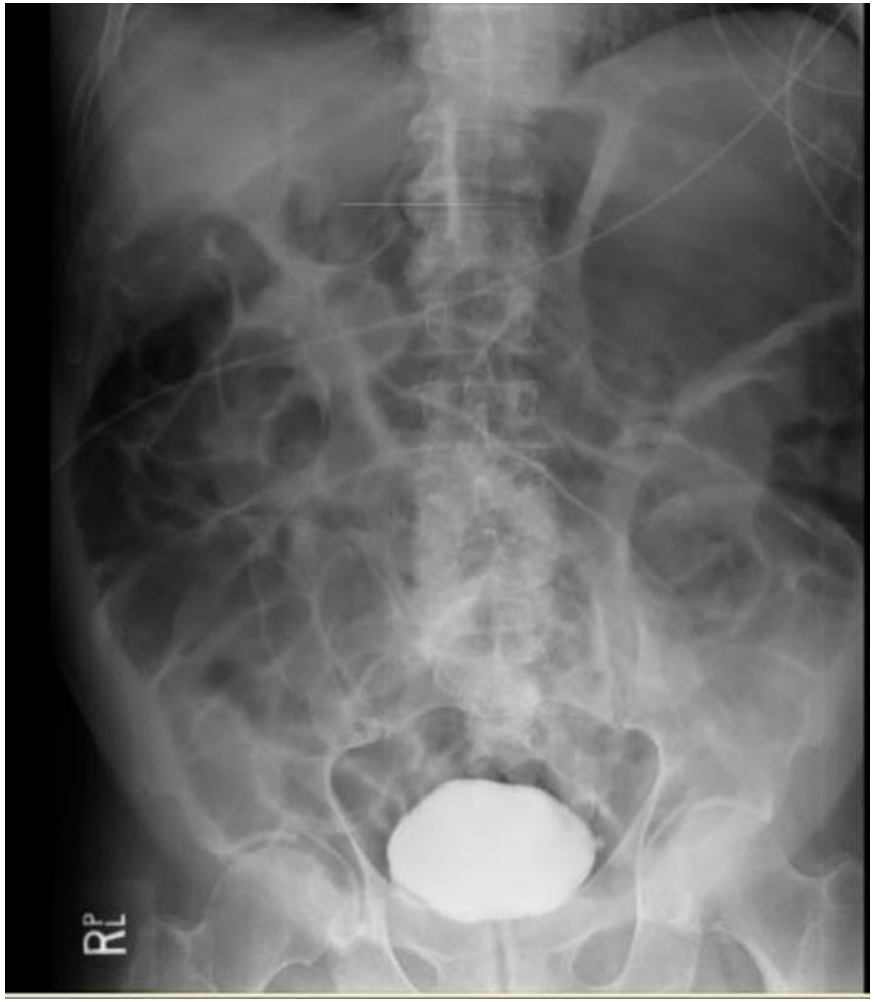
Constipation

- Colonic transit time study:
  - Not prescribed clozapine n=17, CTT 23 h
  - Prescribed clozapine, n=20, CTT 104.5 h
- Ileus
  - May occur with prolonged exposure in a level-dependent fashion
    - Median time to developing ileus was 1528 days
  - Clozapine associated with a 2X risk of ileus, 7X risk of fatal ileus

https://radiopaedia.org/articles/adynamic-ileus



Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, Ellis PM. Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study. EBioMedicine. 2016 Mar;5:125-34. PMID: 27532076.

Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. Schizophr Bull. 2012 May;38(3):592-8. doi: 10.1093/schbul/sbq137. Epub 2010 Nov 26. PMID: 21112965; PMCID: PMC3329981.

Constipation

- Prevention
  - Reduce opioids, iron (if not needed) and anticholinergics
  - Encourage activity
  - Hydration
  - Avoid bulk laxatives like psyllium
- Education
  - Educate staff, family, patient!!
  - Have patients tell you if the frequency of bowel movements changes

Shirazi, A., Stubbs, B., Gomez, L., Moore, S., Gaughran, F., Flanagan, R. J., . . . Lally, J. (2016). Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. *International journal of molecular sciences, 17*(6), 863.

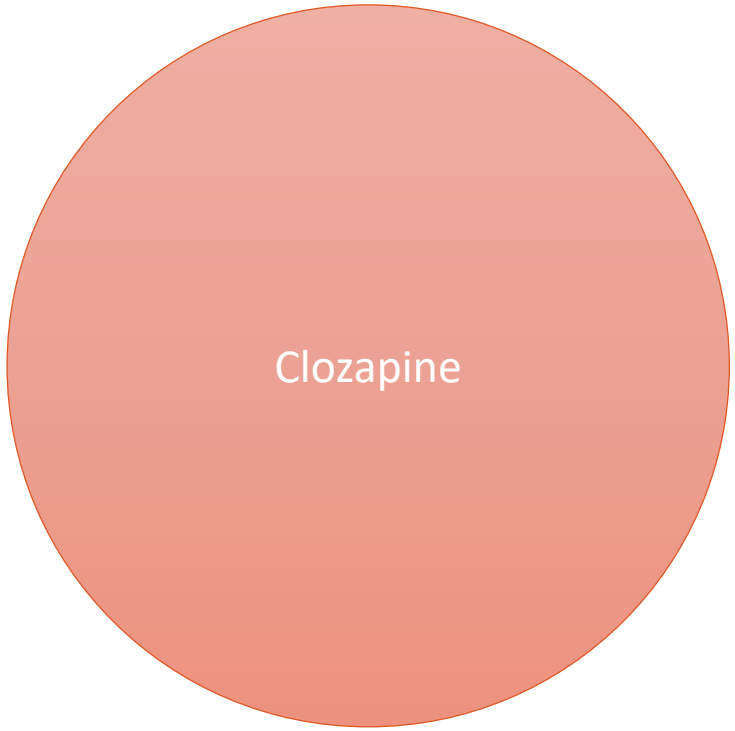
Every-Palmer, S., Ellis, P. M., Nowitz, M., Stanley, J., Grant, E., Huthwaite, M., & Dunn, H. (2017). The Porirua Protocol in the Treatment of Clozapine-Induced Gastrointestinal Hypomotility and Constipation: A Pre- and Post-Treatment Study. *CNS Drugs, 31*(1), 75-85.

Recommended Bowel Regimen

- Step 1: Prophylactic docusate 250 mg BID with rescue PRN
  - Mag citrate 150 ml or magnesium hydroxide 30 ml q 2 days without bowel movement
- Step 2: add one osmotic laxative
  - (e.g. polyethylene glycol 17 gm qam)
- Step 3: add one stimulant laxative
  - (e.g. sennosides 17.2 mg, max 34.4 mg BID) or bisacodyl starting at 5 mg qhs (max 30 mg per day)
- Step 4: add a secretogogue with consideration of tapering other agents
  - (e.g. linaclotide, lubiprostone)

Constipation Management Protocol for Clozapine Treated Patients. California Department of State Hospitals. Nov 2020. Used with permission from Dr. Jonathan Meyer

Hyperphagia



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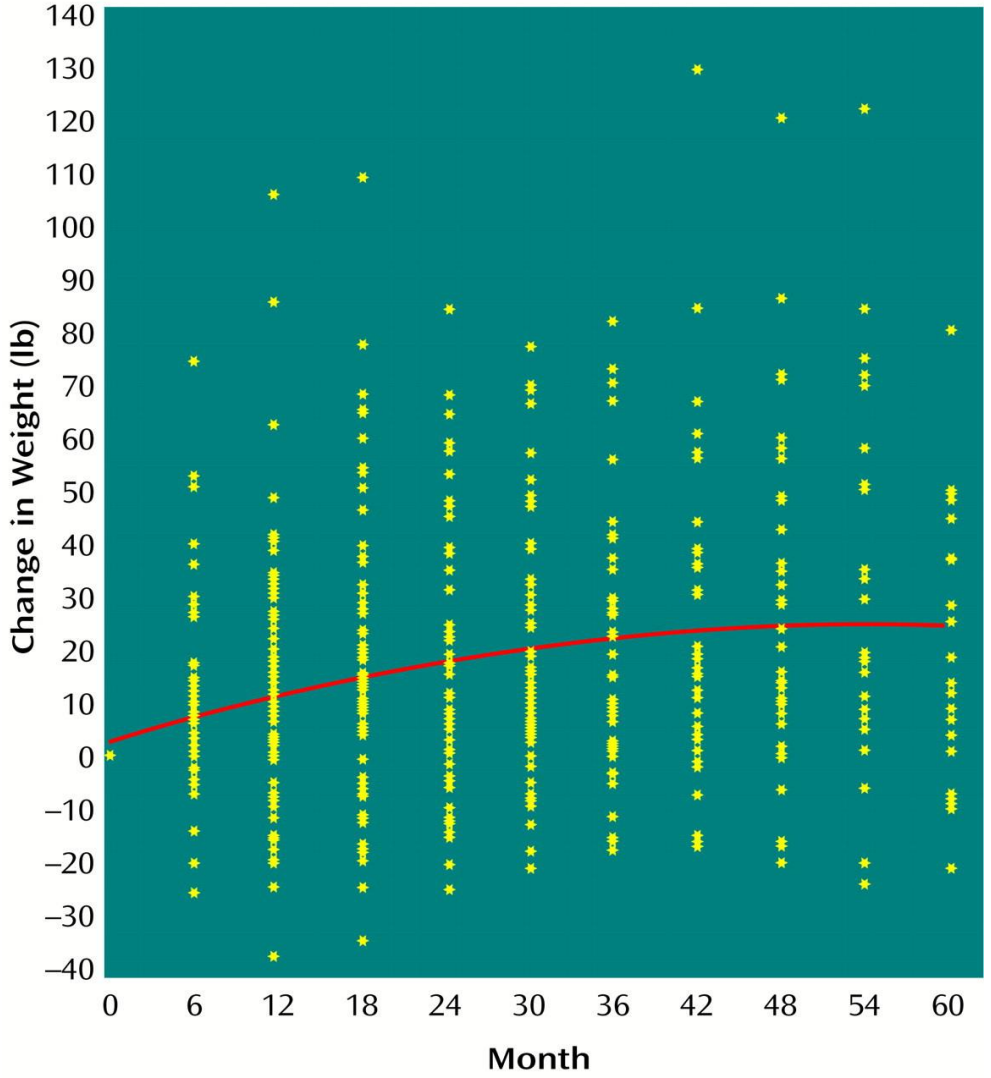
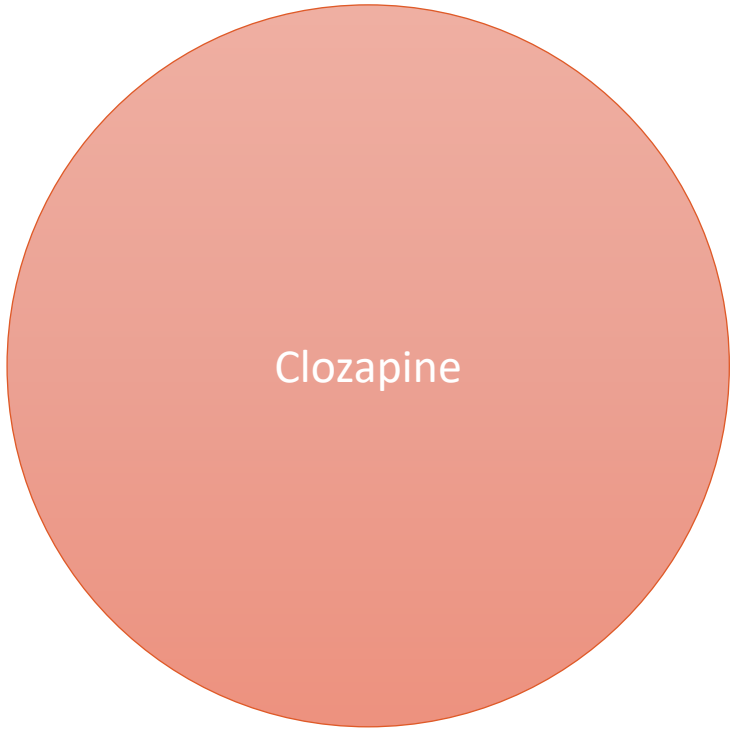
Cardiometabolic Side Effects

- Five-year naturalistic study (N=82)
  - Weight gain finally plateaued at 4th year
  - 367% developed diabetes
- Exceed minimum thresholds established by APA/ADA guidelines
- May correlate with increasing norclozapine levels
- Management
  - Taper/discontinue other contributors
  - Metformin best studied (-3.12 kg v PBO)
  - Others: orlistat, topiramate, naltrexone-bupropion, liraglutide, exenatide



Siskind, D. J., Leung, J., Russell, A. W., Wysoczanski, D., & Kisely, S. (2016). Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis. *PLoS One, 11*(6), e0156208. doi:10.1371/journal.pone.0156208. Henderson, D. C., Cagliero, E., Gray, C., Nasrallah, R. A., Hayden, D. L., Schoenfeld, D. A., & Goff, D. C. (2000). Clozapine, Diabetes Mellitus, Weight Gain, and Lipid Abnormalities: A Five-Year Naturalistic Study. *American Journal of Psychiatry, 157*(6), 975-981. doi:10.1176/appi.ajp.157.6.975. Tan, M. S. A., Honarparvar, F., Falconer, J. R., Parekh, H. S., Pandey, P., & Siskind, D. J. (2021). A systematic review and meta-analysis of the association between clozapine and norclozapine serum levels and peripheral adverse drug reactions. *Psychopharmacology (Berl)*. doi:10.1007/s00213-020-05746-y

Sialorrhea



Drug			M2
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Risperidone	3	5	>10,000
Olanzapine	14		622

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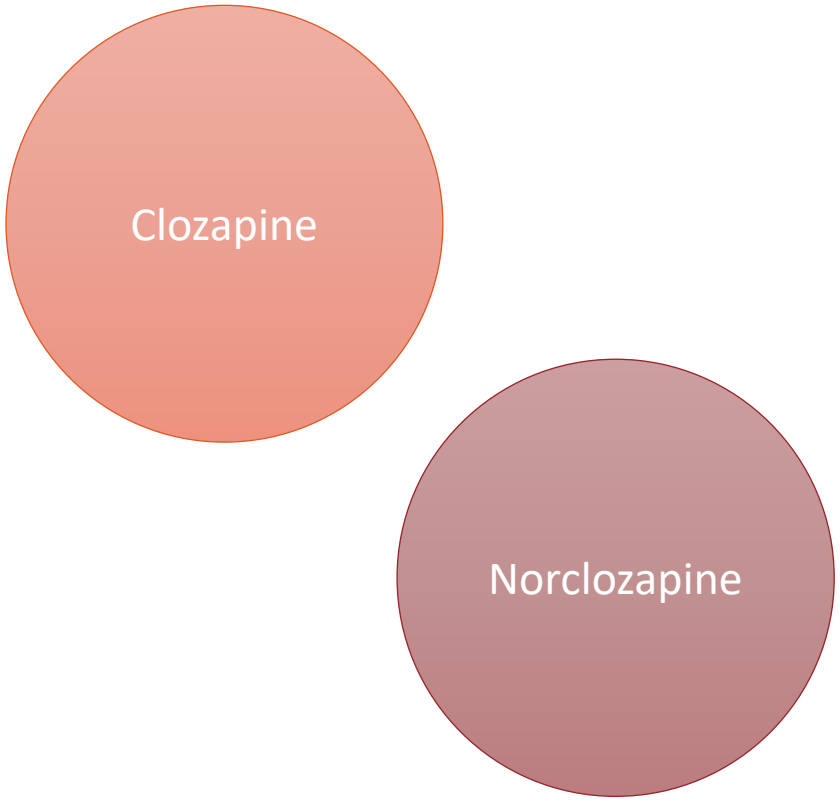
Sialorrhea



- Mechanism incompletely understood
- Salivary glands express M1 and M3 receptors
- Clozapine
  - Agonist at M4
  - α2 antagonist
- Norclozapine
  - Potent M1 agonism

Solmi, M., Murru, A., Pacchiarotti, I., Undurraga, J., Veronese, N., Fornaro, M., . . . Carvalho, A. F. (2017). Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag, 13*, 757-777. doi:10.2147/TCRM.S117321

Sialorrhea

- Common and often bothersome
- Caused by decreased swallowing, leading to increased saliva in the mouth
- Usually not dangerous, but may be an association with pneumonia
- Usually happens while sleeping, sometimes during the day.
- Management
  - Sleep with a towel on their pillow
  - Chew sugarless gum
  - Ophthalmic atropine, ipratropium spray, glycopyrrolate, botulinum toxin

Meyer, J.M. & Stahl, S.M. (2020). *The clozapine handbook.* Cambridge University Press.

Conclusions

Conclusions

- Treatment-resistant schizophrenia is a major public health issue for which clozapine is the clear antipsychotic of choice, and if recognized, treatment should not be delayed.
- Clozapine has a complex and incompletely understood mechanism of action, but its unique properties provide insights into its unparalleled efficacy and into the etiology of schizophrenia.
- An understanding of the pharmacokinetic and pharmacodynamic properties of clozapine can help to optimize its safe and effective use.

THANK YOU!

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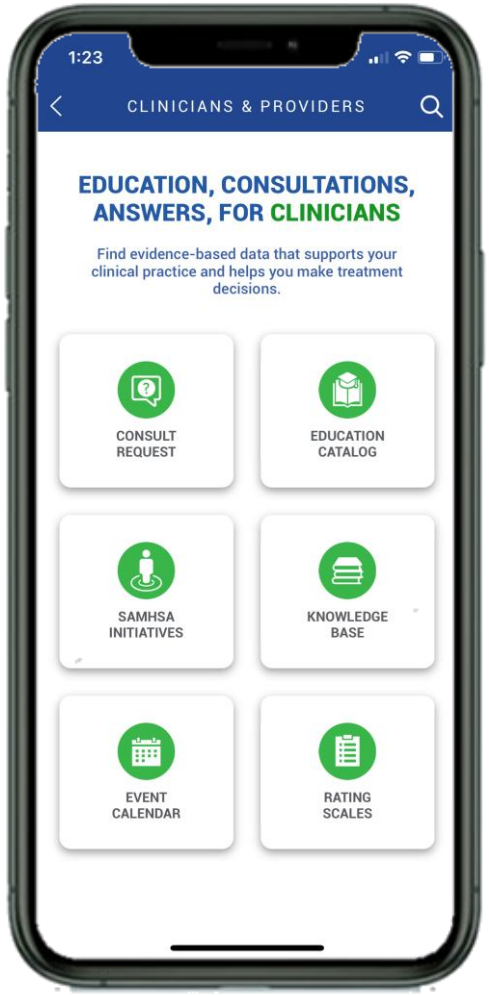

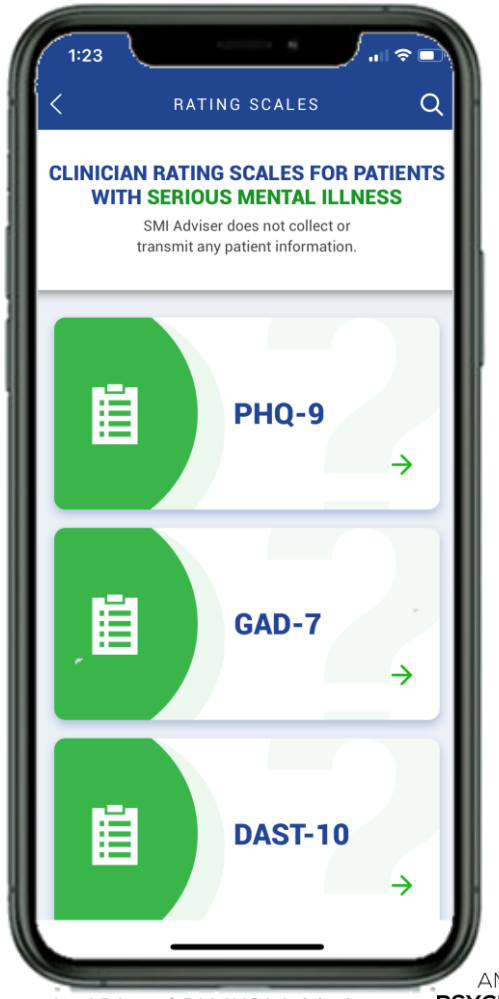

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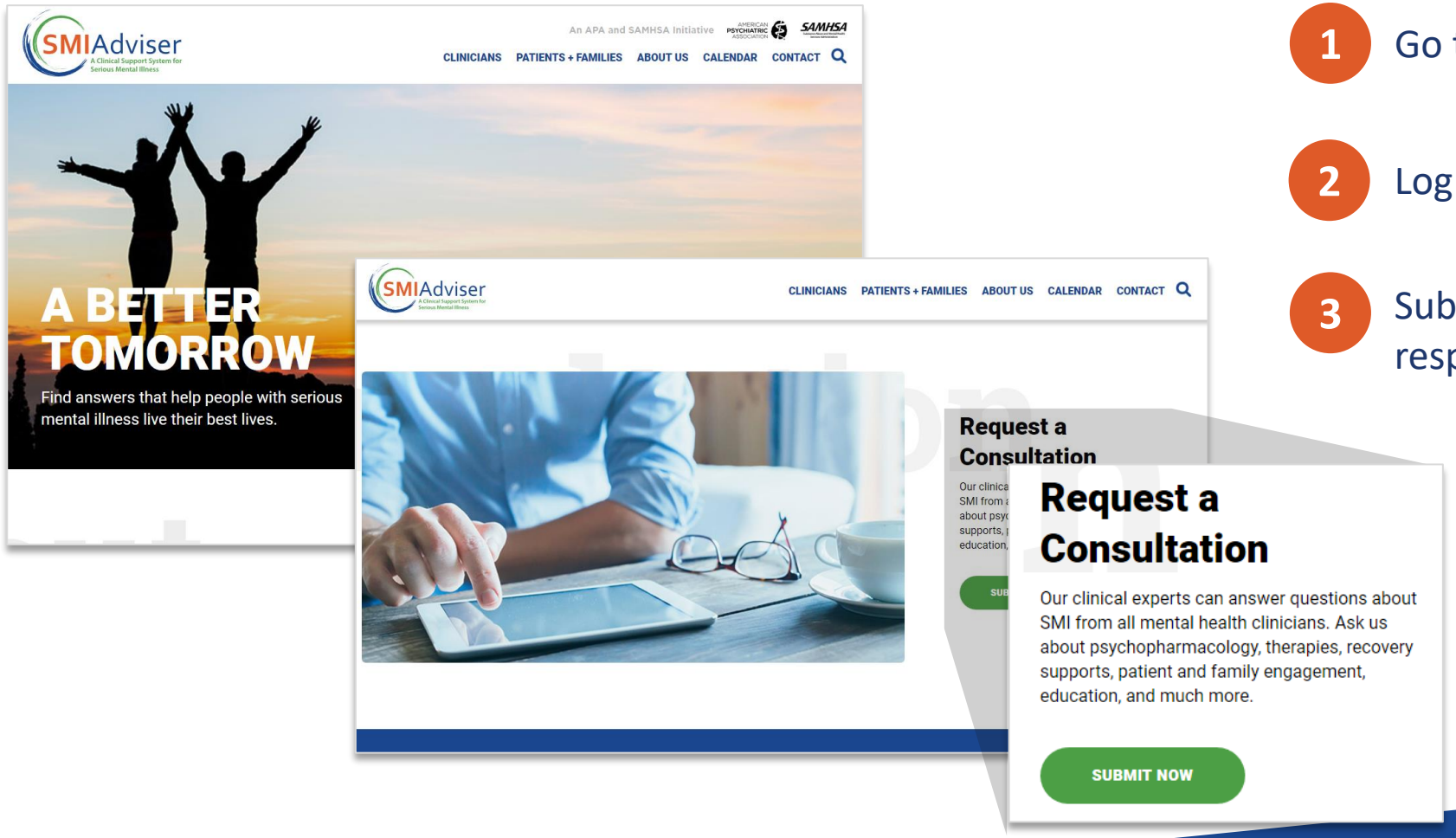

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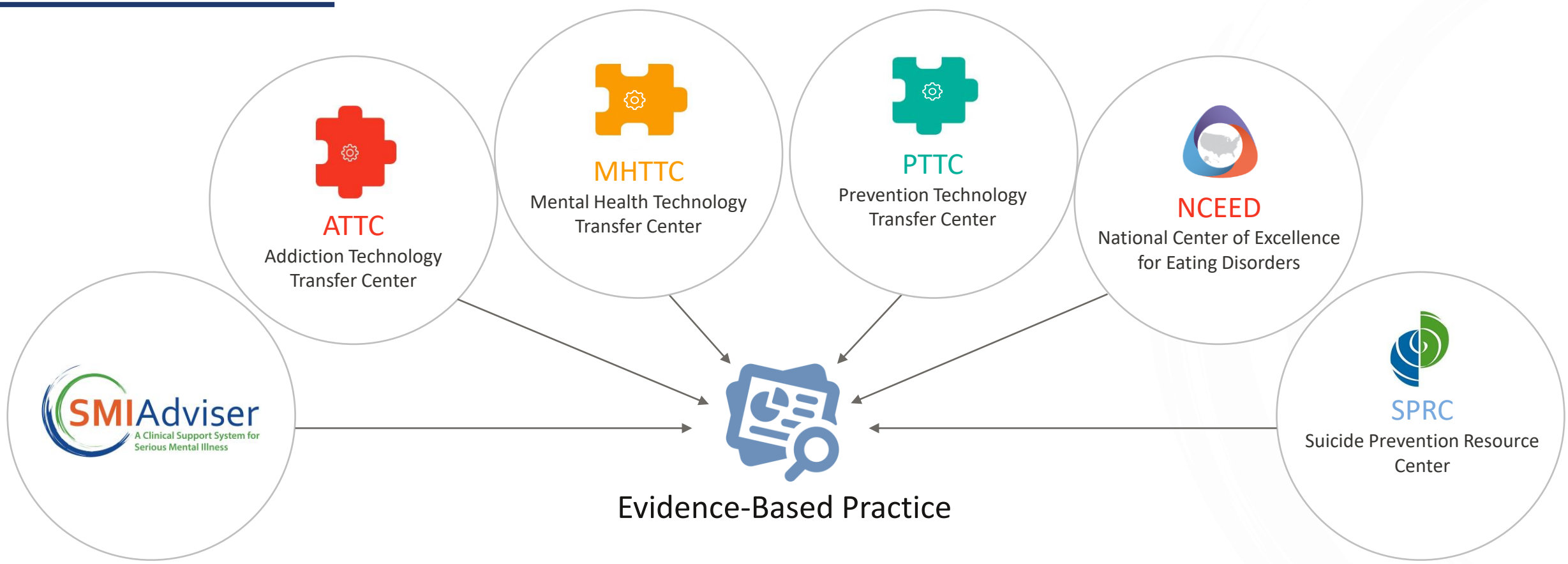

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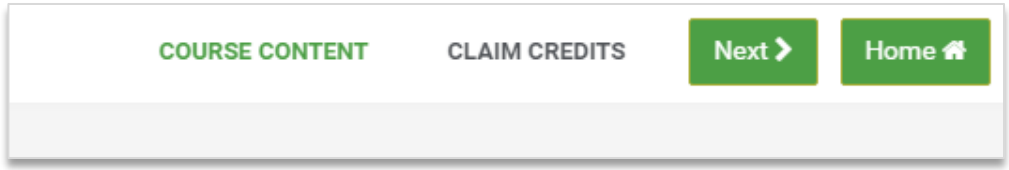

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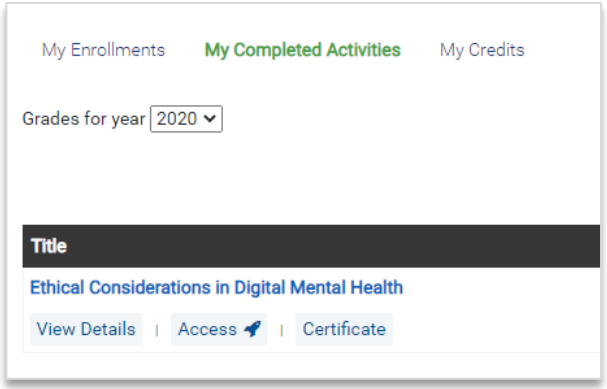

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Bipolar and Alcohol Use Disorder: Break the Magnetic Force!

July 23rd | 12 – 1 pm EST

Javier Ballester-Gonzalez, MD

Reviews the epidemiology of the association of concurrent bipolar and alcohol use disorders.

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