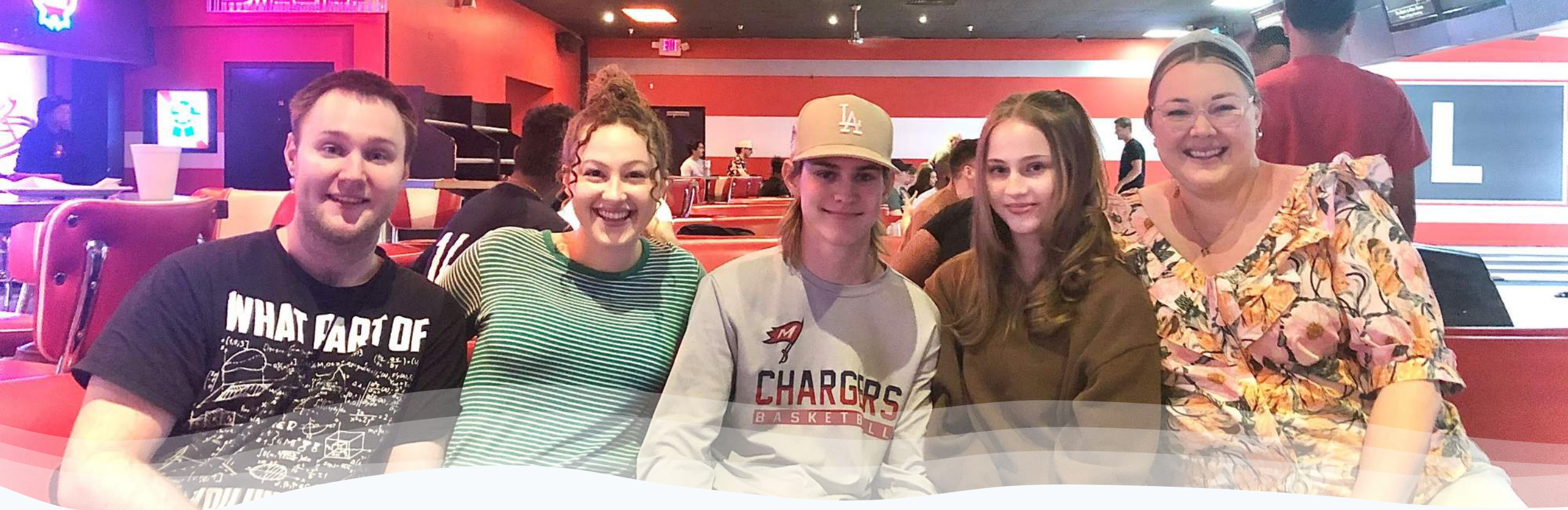
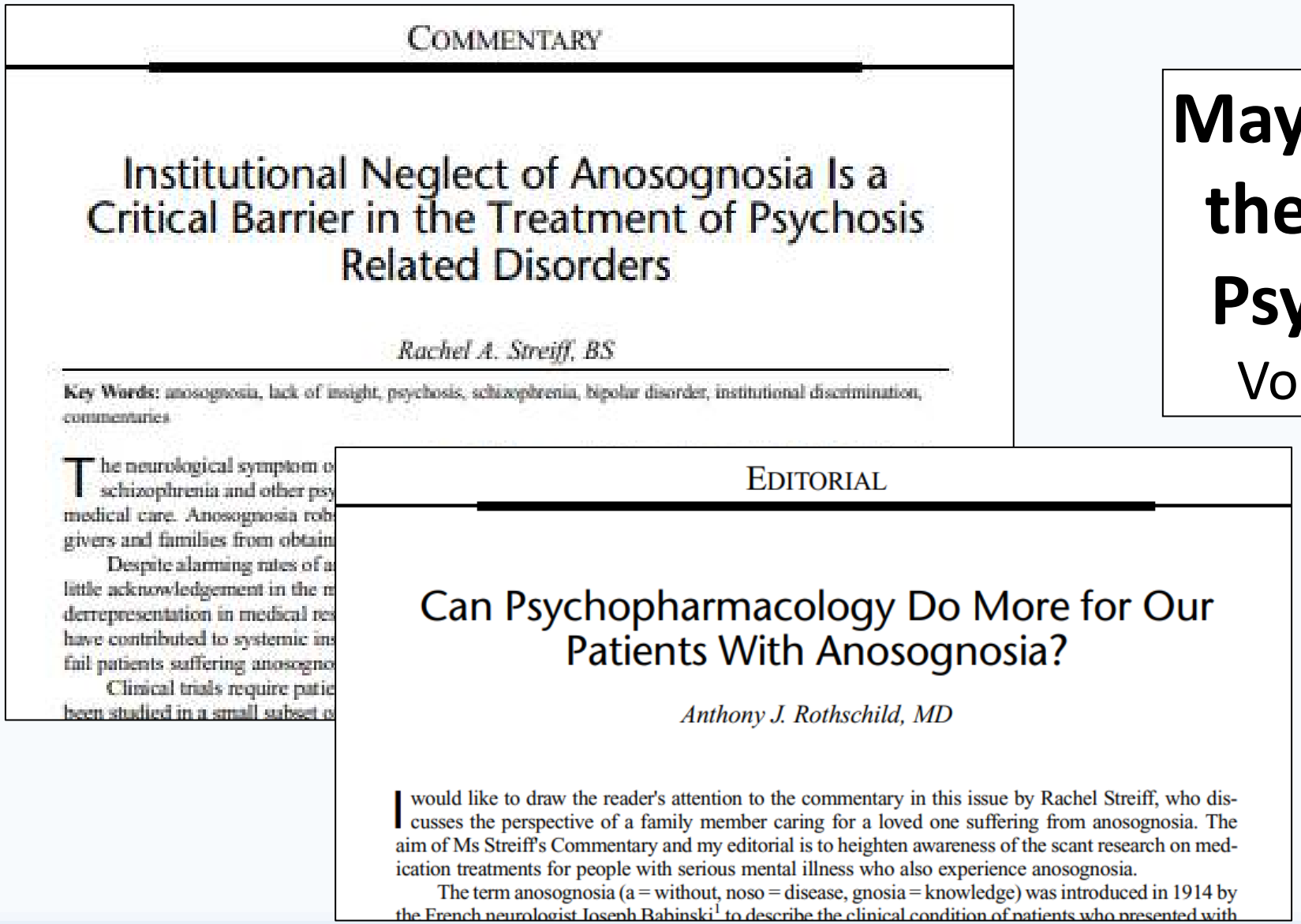


Rachel A. Streiff

Chemical and Biomedical Engineer, Motorola Legacy Six Sigma Black Belt
Data Analyst for Team Daniel Running for Recovery From Mental Illness (remote contractor)
Clinical Assistant for Josiah Nwaokwa, MSN, PMHNP- BC at Psych Zen Health (1 day/week)
Family Mentor for The CureSZ Foundation and Families for Treatment
and

"SMI Mom"

The Most Dangerous Neurological Symptom



COMMENTARY

Institutional Neglect of Anosognosia Is a Critical Barrier in the Treatment of Psychosis Related Disorders

Rachel A. Streiff, BS

Key Words: anosognosia, lack of insight, psychosis, schizophrenia, bipolar disorder, institutional discrimination, commentaries

The neurological symptom o
schizophrenia and other psy
medical care. Anosognosia rob
givers and families from obtain
Despite alarming rates of a
little acknowledgement in the n
derrepresentation in medical res
have contributed to systemic ins
fail patients suffering anosogno
Clinical trials require patie
been studied in a small subset o

EDITORIAL

Can Psychopharmacology Do More for Our Patients With Anosognosia?

Anthony J. Rothschild, MD

I would like to draw the reader's attention to the commentary in this issue by Rachel Streiff, who discusses the perspective of a family member caring for a loved one suffering from anosognosia. The aim of Ms Streiff's Commentary and my editorial is to heighten awareness of the scant research on medication treatments for people with serious mental illness who also experience anosognosia.

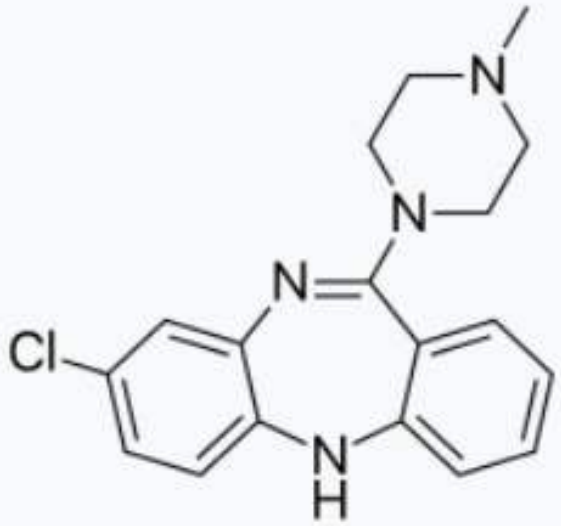
The term anosognosia (a = without, noso = disease, gnosia = knowledge) was introduced in 1914 by the French neurologist Joseph Babinski[1] to describe the clinical condition of patients who presented with

May/June 2023 Issue of the Journal of Clinical Psychopharmacology

Vol. 43 Issue 3 p. 200-203

Plus! Podcast with the editor Dr. Anthony Rothschild and Dr. Julia Koretski.

Clozapine



A Second-Generation Antipsychotic

The ONLY medication FDA-approved for:

- Treatment Resistant Schizophrenia (TRS)
- Reduce the risk of suicidal behavior in younger patients with schizophrenia.

An Amazing Recovery Story

“C”s High School Senior Picture 2018

2019 Onset of illness

- Schizoaffective Disorder with Anosognosia
- Court-Ordered Treatment

Early intervention with clozapine.

“C” in 2023

- Double Major at ASU
- Deans List (4.0 GPA)
- Instructional Design Team at ASU

SYMPTOM FREE

Source: Team Daniel Running for Recovery

Our Daniel

1993

2019

Dedicated Doctors Who Care About Families

Source: Team Daniel Running for Recovery

Dr. Laitman & Team finishing the 2023 Boston Marathon

Saturday get-togethers and Zooms with patients and families.

Source: Team Daniel Running for Recovery

The "Team Daniel" Practice – Clozapine Centered

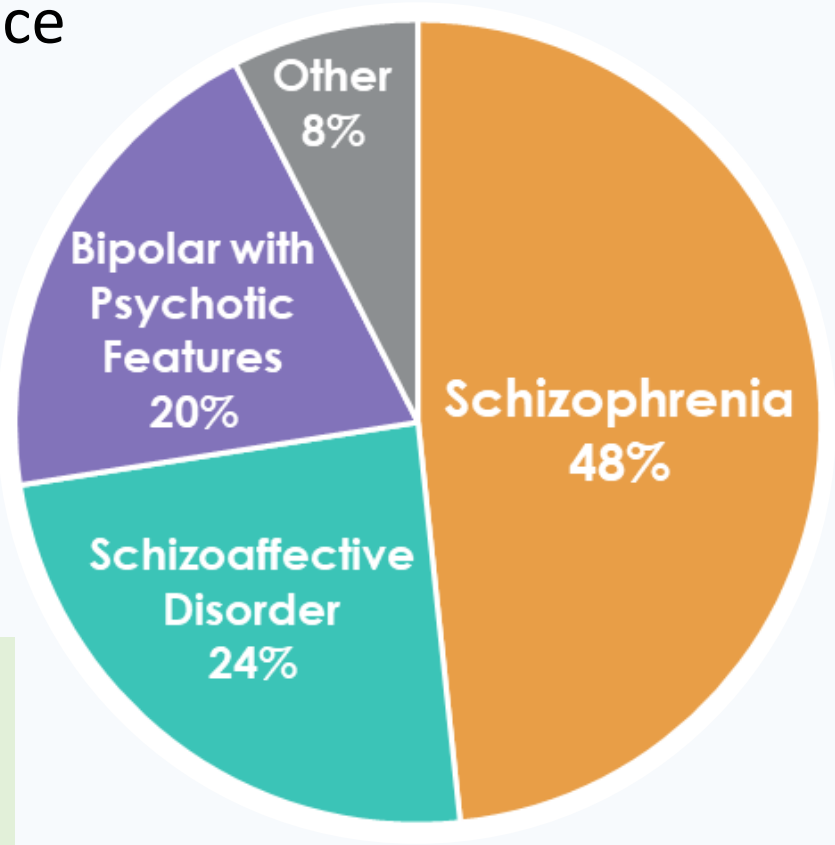
Over **180** clozapine patients with **94%** rate of continuance

Not a "first episode clinic"

(Only 5% are truly "clozapine first")

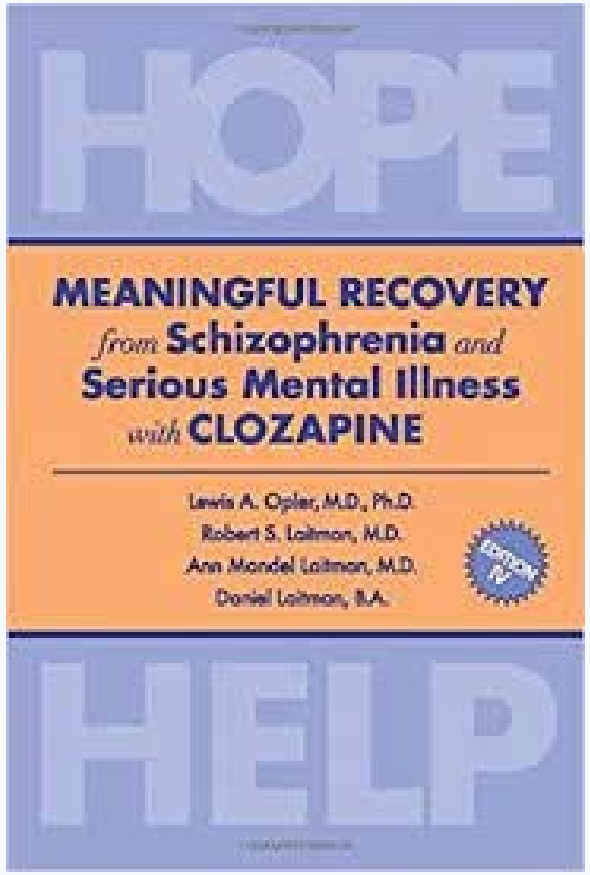
54% are already on clozapine at intake

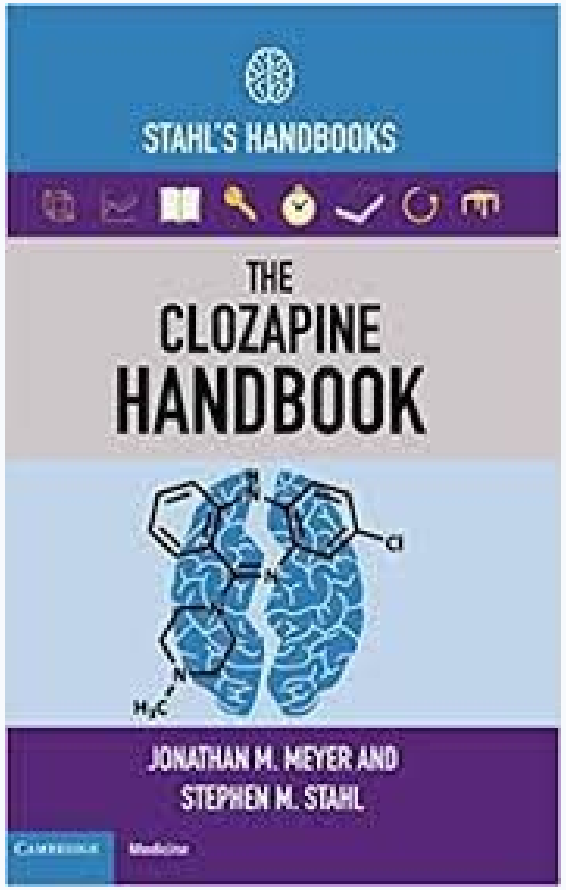
46% are new to clozapine



Dr. Robert Laitman and Dr. Ann Mandel specialize in both "treatment-resistant" and clozapine-resistant patients.

Important Books





Our Journey to Clozapine

Doctor #1 **"It's very dangerous, it is only a last resort"**
"Why would you want that? He's doing well"
(Only reserved for the sickest patients)

Doctor #2 **"We don't do clozapine here"**

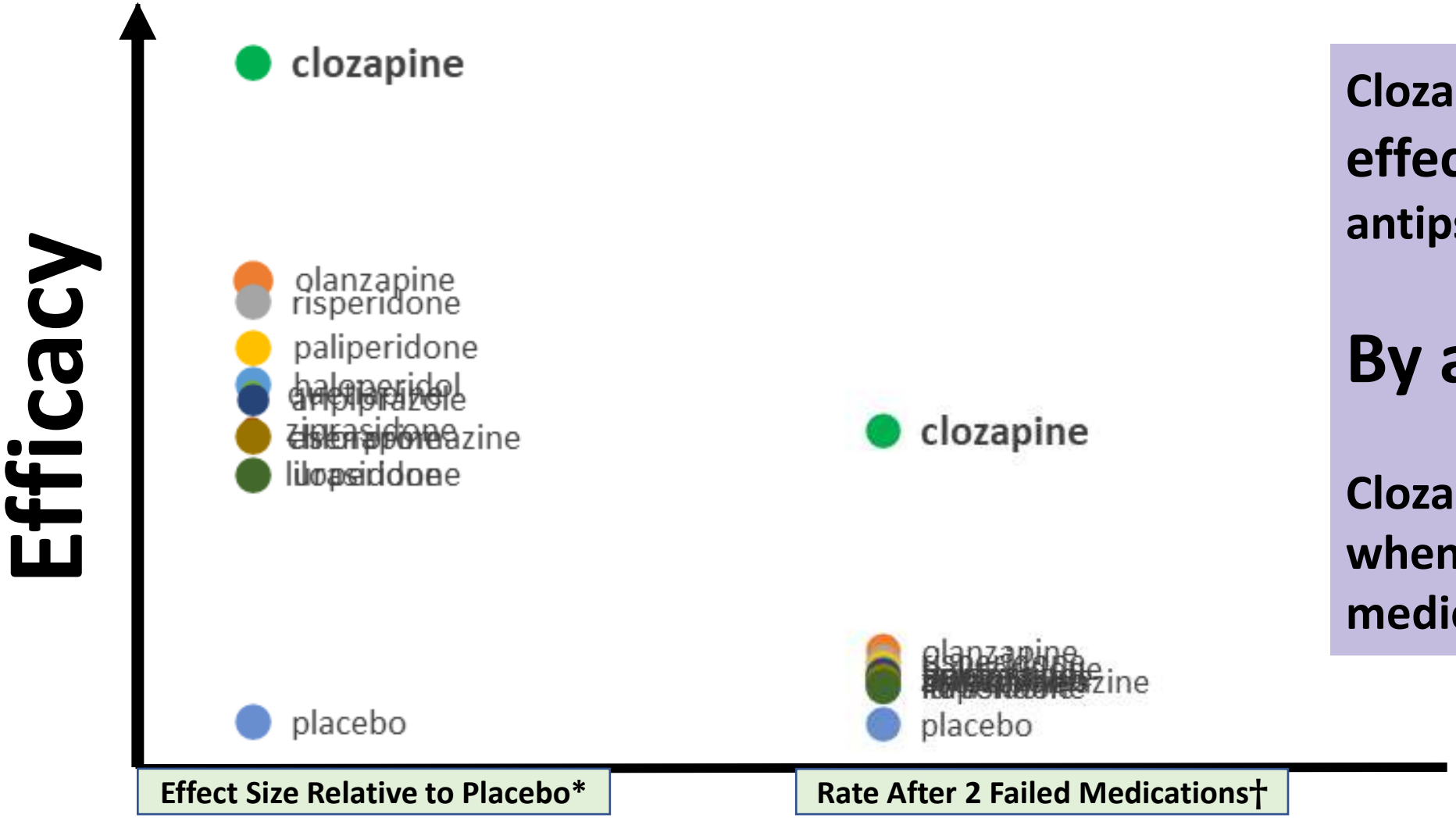
Doctor #3 **"We don't use that anymore, there's newer, better meds now"**

Doctor #4 **"We can't do clozapine with poor insight and non-compliance"**

Doctor #5 **"Yes – I do a lot of clozapine!" (She is 2-hours away)**

Clozapine: The Most Effective Antipsychotic

(Meta Analysis of Over 43,000 individuals)



Clozapine is the most effective antipsychotic…

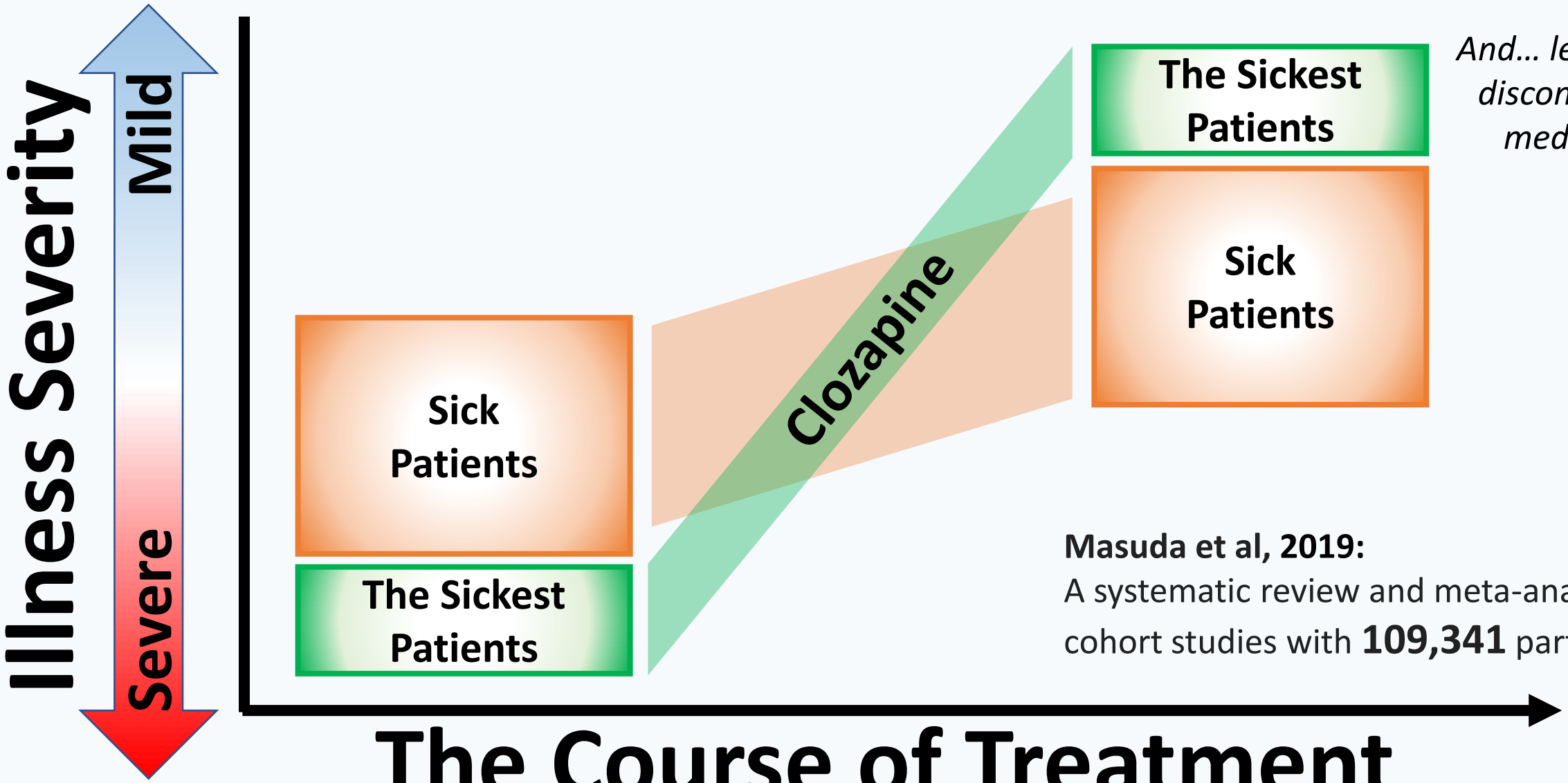
By a lot.

Clozapine often works when other medications fail.

*Leucht S, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013 Sep 14; **382**(9896):951-62

† S Graphical representation combining Leucht, 2013 with Siskind D, et al. Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. *Can J Psychiatry*. 2017 Nov; **62**(11):772-777

Clozapine: Sicker Patients Fare the Best?



And… less likely to discontinue the medication.

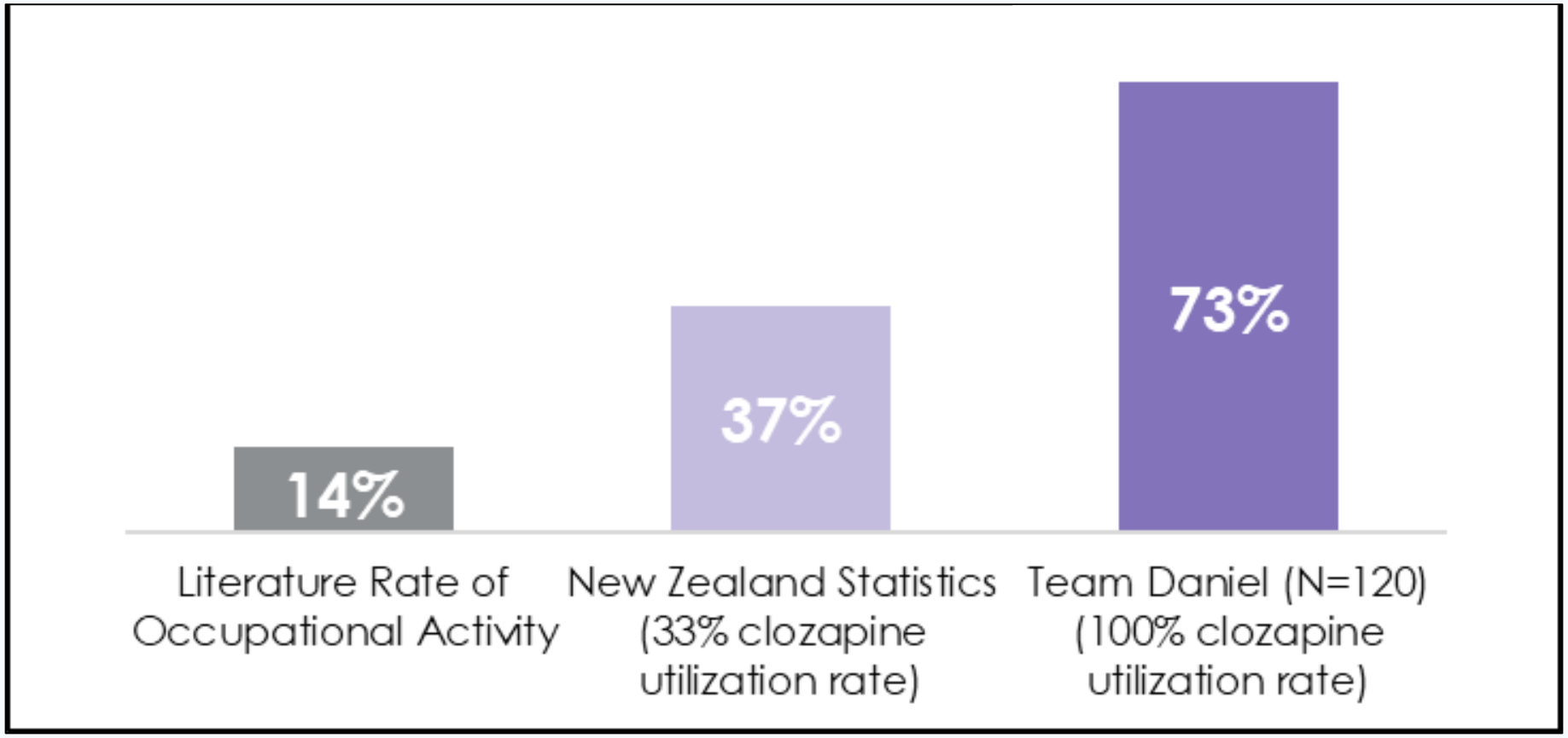
Masuda et al, 2019:
A systematic review and meta-analysis of 63 cohort studies with **109,341** participants.

“Team Daniel” Rate of Meaningful Recovery After 1 Year

TEAM DANIEL©

Source: Team Daniel Running for Recovery

20+ Hours Per Week of School, Work or Meaningful Activity



Source: Laitman, R.L. (2022, March 16) Optimal *Treatment of Psychotic Disorders: Clozapine / Engagement / Community* [Webinar] Team Daniel Running for Recovery From Mental Illness https://www.youtube.com/watch?v=l2QUKbyD4rk

Clozapine: The SAFEST Antipsychotic?

A Finnish 20-year Study of >62,000 Patients with Schizophrenia

"FIN-20" Study: Clozapine reduces ALL CAUSES of mortality and ADDS 10 Years over other antipsychotics.

65% less likely to die than untreated patients with schizophrenia
25% to 50% less likely to die compared patients on other antipsychotics
70-90% reduction in suicide
45% reduction in cardiovascular deaths
The mortality rate for quetiapine is TWICE AS HIGH as clozapine

(Vermeulen JM, et al, 2019; Taipale H, et al (FIN20), 2020; Hayes RD, et al, 2015; Wimberley T, et al, 2017)

Patients FEEL Better

Patients Stay on Clozapine More than Any Other Antipsychotic

Minimal Movement Disorders (EPS) 

No Prolactin Increase 

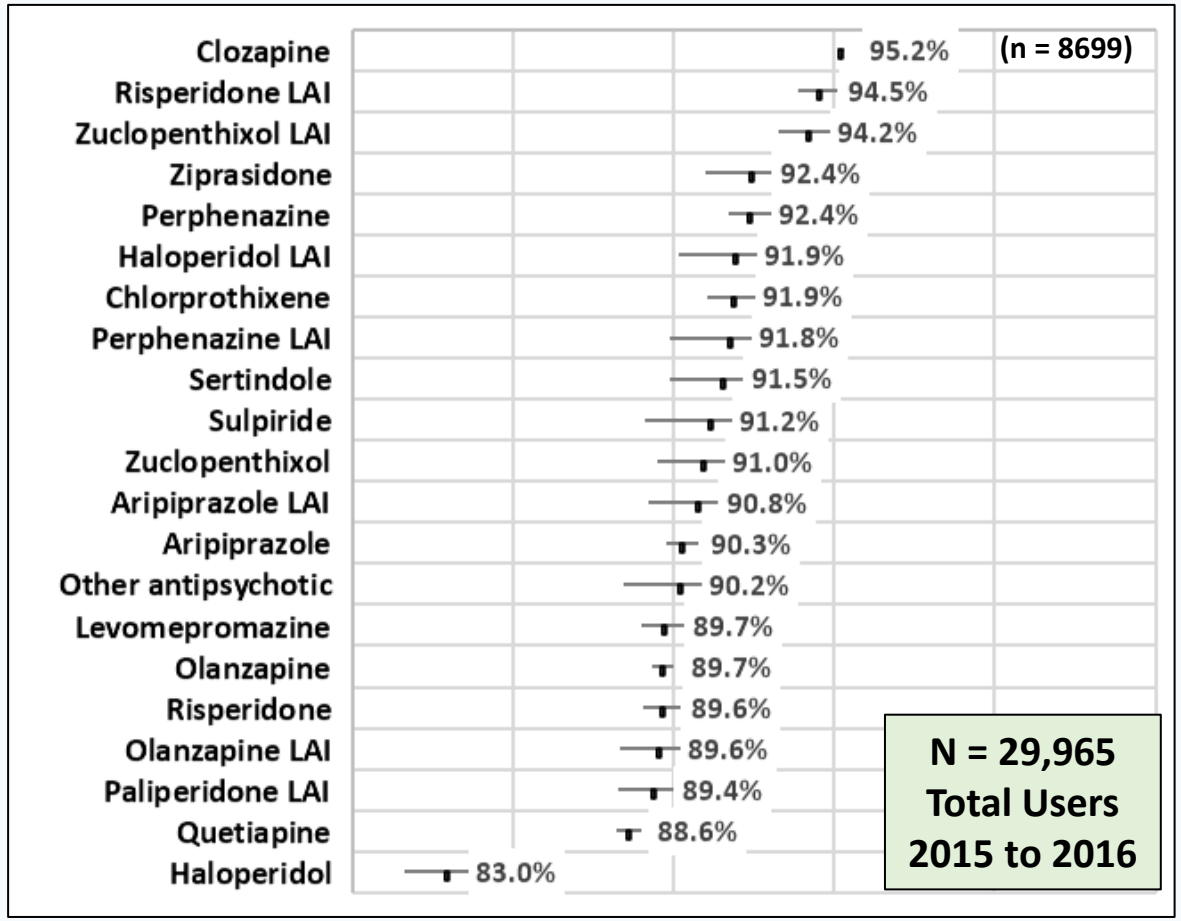
No Erectile Dysfunction 

Minimal Dopamine Blocking 

Severe risks, including cardiovascular, neuroleptic malignant syndrome, diabetes and *even agranulocytosis* are comparable to other antipsychotics.

Higher Adherence Than Any Other Antipsychotic

Dispensed Proportion of Prescriptions Issued

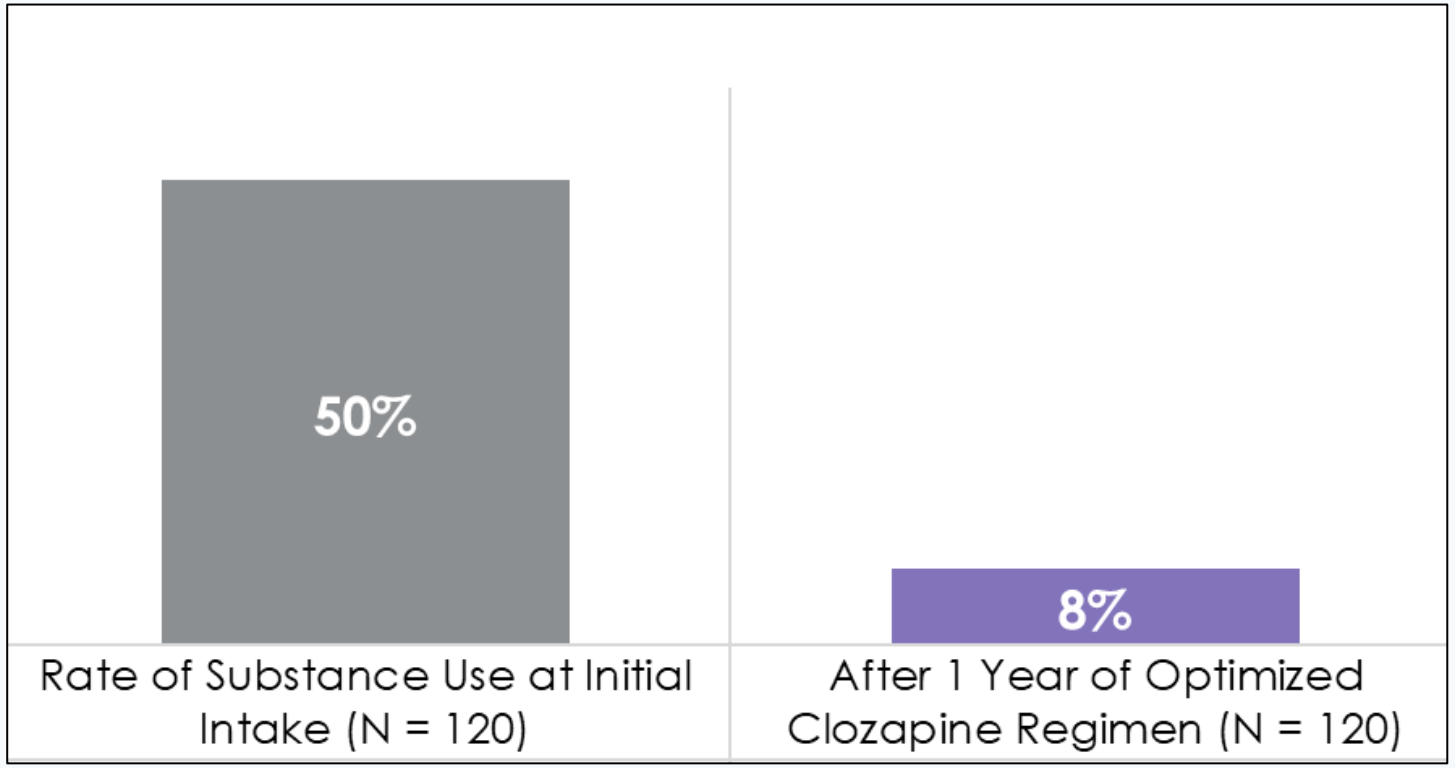


Patient adherence to clozapine is better than any other antipsychotic, ***including long-acting injectables.***

Finnish registry
29% clozapine utilization
(Lieslehto J, et al, 2022)

Source: Team Daniel Running for Recovery

Clozapine: SUD Recovery Rate Unprecedented



82% Recovery from Substance Use

82% Recovery from Cannabis Use Alone

RATE OF SUBSTANCE USE DISORDER

Cannabis was the primary drug in 85% of patients

Expected Rate of Clozapine Use

30% of patients with schizophrenia are "treatment-resistant"

APA guidelines after two failed antipsychotics

Australia	35%
New Zealand	33%
China	30%
England	23%
Sweden	22%
Germany	20%

(Treatment Advocacy Center, 2016)

Woeful Underutilization in the US

In the United States less than 4% of patients are treated with clozapine.

Current Utilization Rate in the US

Third world countries use more clozapine than the United States

(Treatment Advocacy Center, 2016)

The American Clozapine Gap

500,000

Undertreated Individuals with TRS

The American Clozapine Gap

Over 500,000 people who should be seeing the benefits of clozapine but are instead being treated with ineffective medications.

(Messamore, 2021)

Deadly Failure to Use Clozapine

Equates to 2500 deaths per year

25% to 60% of these deaths are suicides.

Due to increased mortality rate of inferior antipsychotics.

(Vermeulen JM, et al, 2019; Taipale H, et al (FIN20), 2020; Hayes RD, et al, 2015; Wimberley T, et al, 2017)

Doctors Fail to Follow APA Guidelines

Average duration to clozapine trial: ***4 to 8 years***

Mean number of failed antipsychotics: **3 to *5***

Polypharmacy: 20%

Clozapine: **4% - *this is not the standard of care***

This is an unacceptable failure to treat our sickest and most vulnerable patients.

(Howes OD, 2012; Alessi-Severini S, 2014: Nielsen J, 2012; Goren, 2013; Gallego JA, 2012)

Impact of Delays in Commencing Clozapine

The Critical Treatment Window:

Response rate if initiated within 2.8 years: **82%**

Response rate after 2.8 years: **31%**

Yoshimura, 2017 (N = 105)

Time = Brain

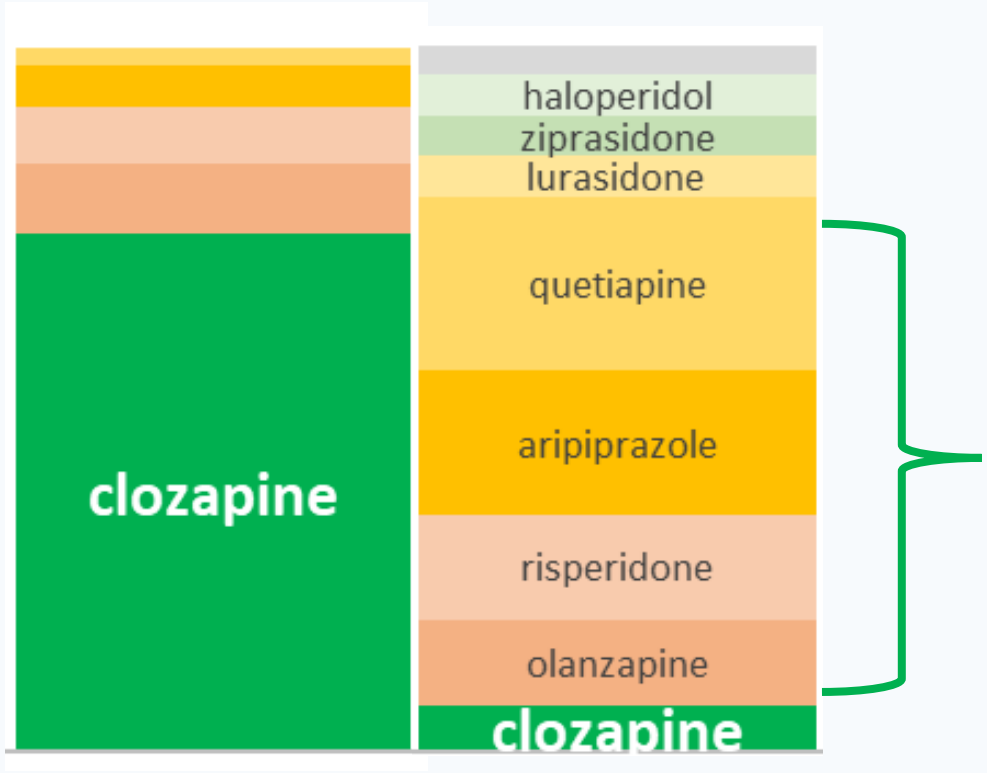
"The extent of delay in starting clozapine was an independent contributor to the odds of clozapine response"

Ucok, 2015 (N = 162)

Üçok A, Çikrikçili U, Karabulut S, Salaj A, Öztürk M, Tabak Ö, Durak R. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2015 Sep;30(5):290-5

Bunta Yoshimura, Yuji Yada, Ryuhei So, Manabu Takaki and Norihito Yamada, The critical treatment window of clozapine in treatmentresistant schizophrenia: secondary analysis of an observational study, *Psychiatry Research*, http://dx.doi.org/10.1016/j.psychres.2017.01.064

The American Clozapine Gap Might Be Much Bigger



Potential for Early Intervention

Silver Hill Hospital, CT
Viewpoint Dual Recovery, AZ
Team Daniel (Dr. Laitman & Dr. Mandel)

Some successful programs are using clozapine at a much higher rate.

(Laitman, 2022)

Why is Clozapine Underused?

~~Efficacy~~

~~Safety~~

~~Tolerability~~

It is Inconvenient

The (Many) Inconveniences of Clozapine

1. Excessive “mandatory” blood tests
2. No long-acting injectable
3. Adjunctive medications are required
   (more so than other antipsychotics – requires internal medicine)
4. Consistency is required
   (more so than other antipsychotics)
5. No standard dose; requires serum levels
6. *The product label and prescribing guidelines are dangerously outdated.*
7. It takes a long time to work (months, sometimes years)
8. Strong interaction with tobacco smoke
9. Increased need for sleep; up to 12 hours per night.

Optimizing Clozapine For Success

94% Continuance

74% Meaningful Recovery

Eliminate Inconvenience

The Clozapine Label is Outdated

$$\text{The "CD ratio"} = \frac{\text{Clozapine Serum Level (ng/mL)}}{\text{Total Clozapine Dose (mg/day)}}$$

Supplementary table from de Leon's "A Rational Use of Clozapine" (2020)

Table S1. Current[a] recommendations for average clozapine maintenance doses. In the absence of TDM access, if the patient does not respond to the recommended average dose, add 50 mg/day extra. Do not use fluvoxamine without TDM[b]

CD ratio	7	3.50	2.33	1.75	1.40	1.17	1.00	0.86	0.78	0.70	0.64	0.58	0.54	0.50	0.47	0.44	0.42	0.39
D	50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900
Asians (ancestral origin ranging from Pakistan to Japan and possibly the original inhabitants of the Americas)																		
			ns♀	s♀	ns♂	s♂												
Inhibitor[c]	ns♀	s♀	ns♂	s♂														
Obese[d]	ns♀	s♀	ns♂	s♂														
Inducers[e]						ns♀		s♀		ns♂		s♂						
US Caucasians[f] and African-Americans																		
						ns♀		s♀		ns♂		s♂						
Inhibitor[c]			ns♀	s♀	ns♂	s♂												
Obese[d]	ns♀	s♀	ns♂	s♂														
Inducers[e]									ns♀		s♀				ns♂			s♂[g]

Jose de Leon et al., "A Rational Use of Clozapine Based on Adverse Drug Reactions, Pharmacokinetics, and Clinical Pharmacopsychology" *Psychotherapy and Psychosomatics,* April 14, 2020

The Clozapine Label is Outdated

A person with CD Ratio of 7:

200 mg/day

Serum = 1,400 ng/mL

(likely toxic)

Potential Characteristics (de Leon):
Asian, obese, non-smoking, female

A person with CD Ratio of 0.39:

200 mg/day

Serum = 78 ng/mL

(zero effect)

Potential Characteristics (de Leon):
Caucasian, lean, smoking, male

Reality: *Unpredictable*

Jose de Leon et al., "A Rational Use of Clozapine Based on Adverse Drug Reactions, Pharmacokinetics, and Clinical Pharmacopsychology" *Psychotherapy and Psychosomatics,* April 14, 2020

The Clozapine Label is Outdated

TEAM DANIEL©

Source: Team Daniel Running for Recovery

Total Daily Dose (mg) Increases Per Week

The Clozapine Label is Outdated

"We tried clozapine, but…"

He got really sick
The side effects were terrible
She couldn't move
It didn't work
She just got worse
He got totally psychotic

These problems are a result of outdated prescriber guidelines.

Recent evidence:

- Go ***much*** slower
- Treat side effects
- Measure serum levels

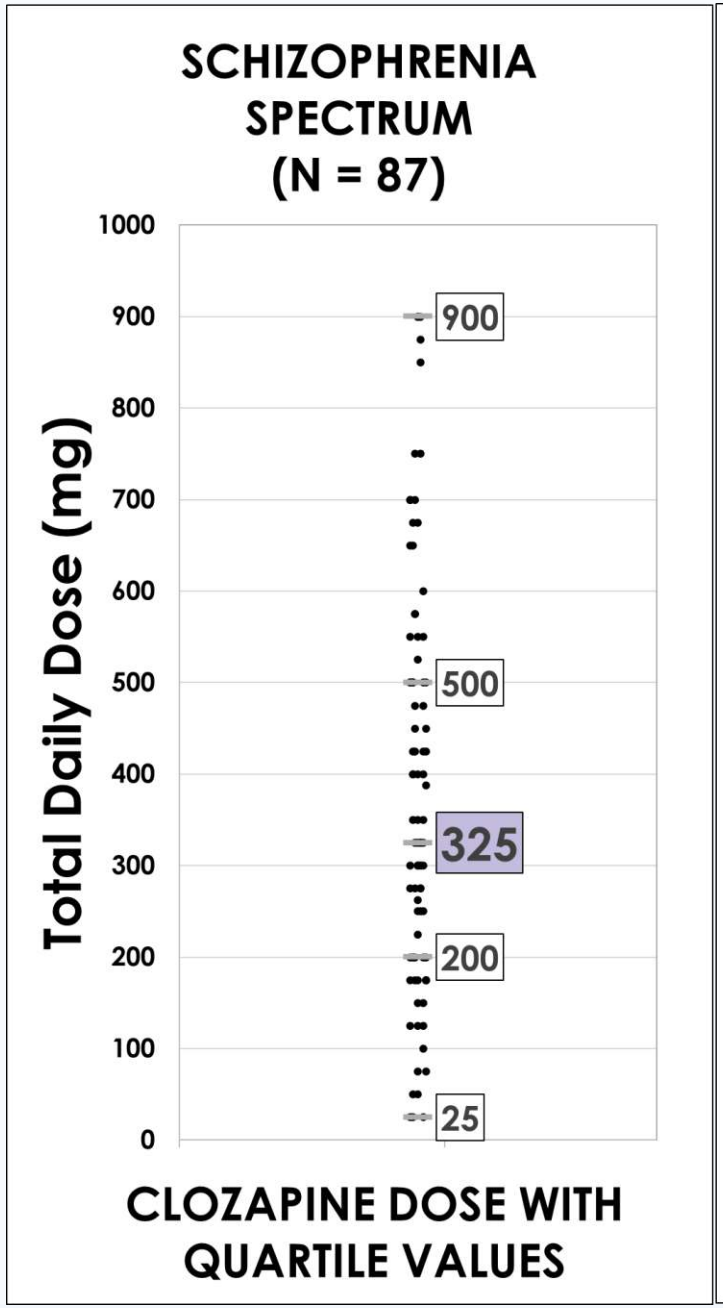
A dangerous practice: Hospitals titrate way too fast in an effort move patients quickly

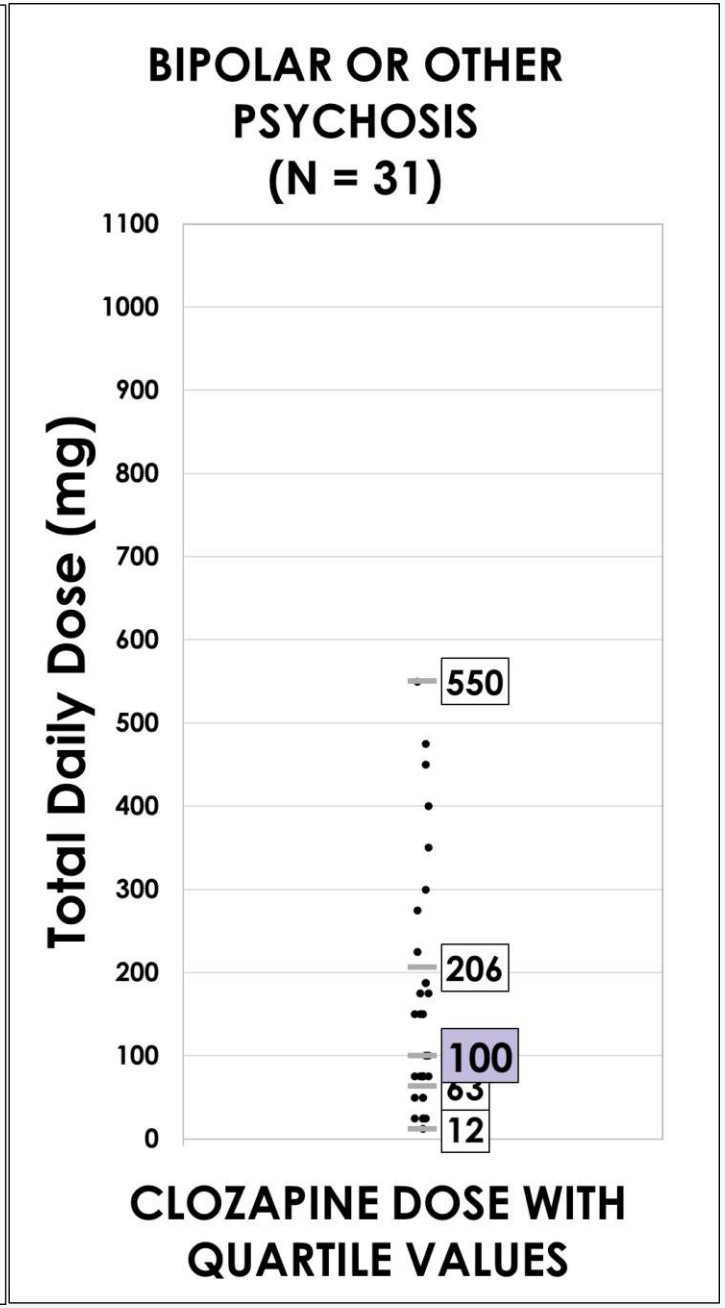
The Clozapine Label is Outdated

Titrating too fast:

- Myocarditis
- Severe orthostasis
- Body Pain
- Seizure
- Bowel Blockage
- Severe drooling => aspiration pneumonia
- Tachycardia (with anxiety)
- Severe sedation
- Vomiting
- Neuroleptic Malignant Syndrome
- …Even Neutropenia

Source: Team Daniel Running for Recovery





TOTAL DAILY CLOZAPINE DOSE (mg) AFTER 1 YEAR

(N = 118)*

*2 patients symptoms resolved

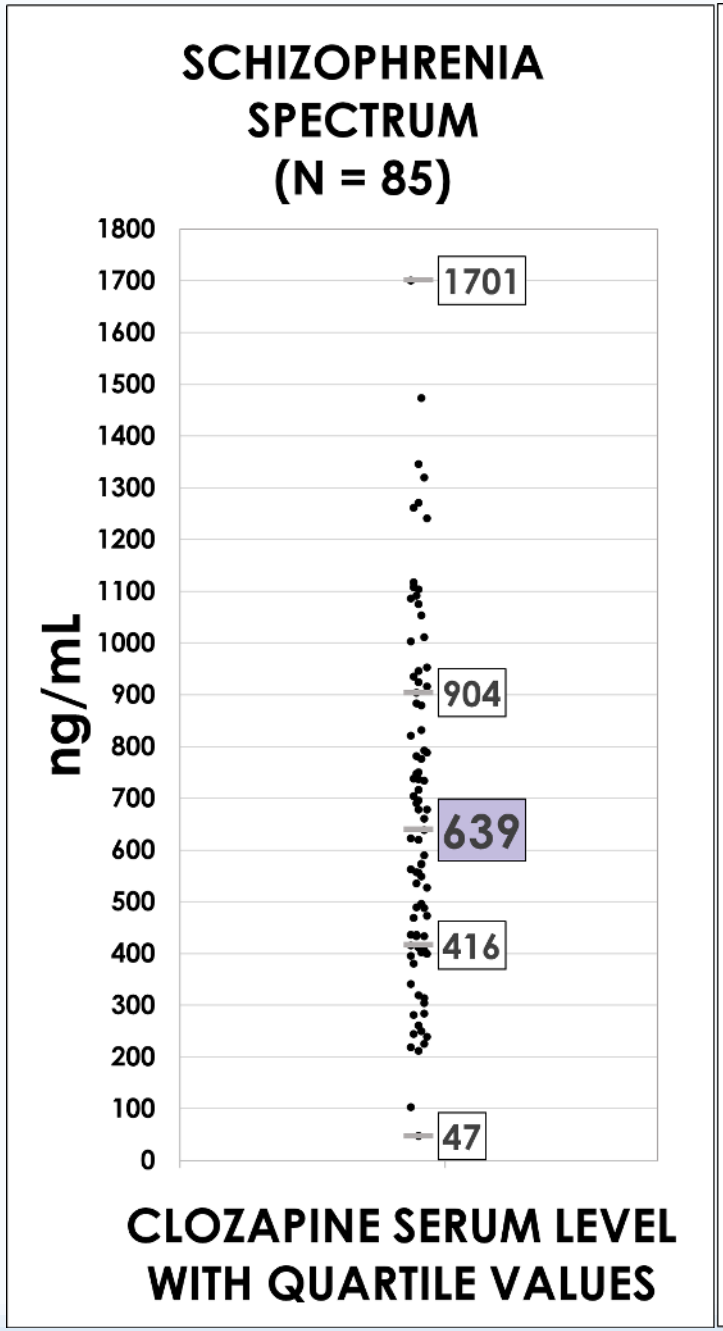
Note:

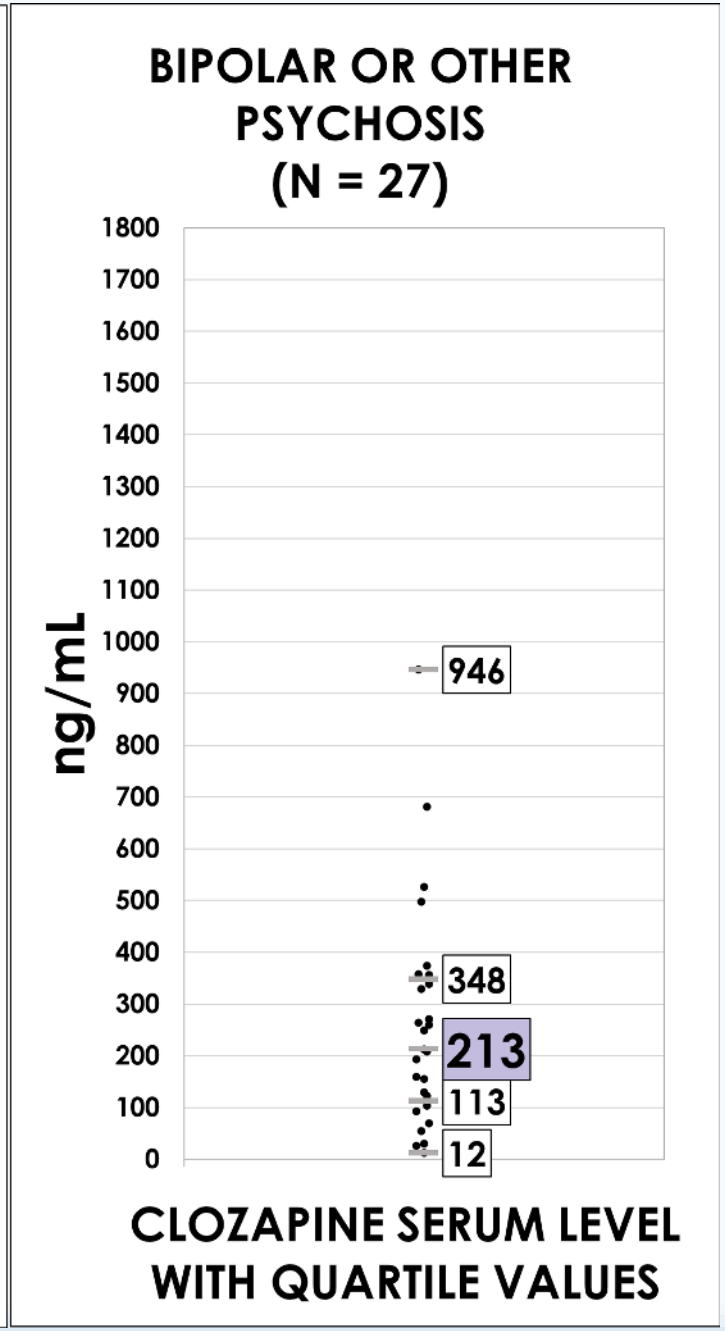
Many patients have clozapine levels augmented with fluvoxamine which allows a lower dose to be used.

There is no standard dose:

Use TDM and patient symptoms to determine dose.

Source: Team Daniel Running for Recovery





THERAPEUTIC CLOZAPINE SERUM LEVELS (ng/mL) AFTER 1 YEAR

IN PATIENTS WITH DETECTABLE LEVELS (N = 112)*

*8 patients with no detectable levels

Push Boundaries:

Literature therapeutic range:
350 to 650 ng/mL
Traditional Upper Limit:
1000 ng/mL

Most TEAM DANIEL patients are on anti-seizure medications.

Treating & Preventing Side Effects is Vital to Treatment

Before the Illness

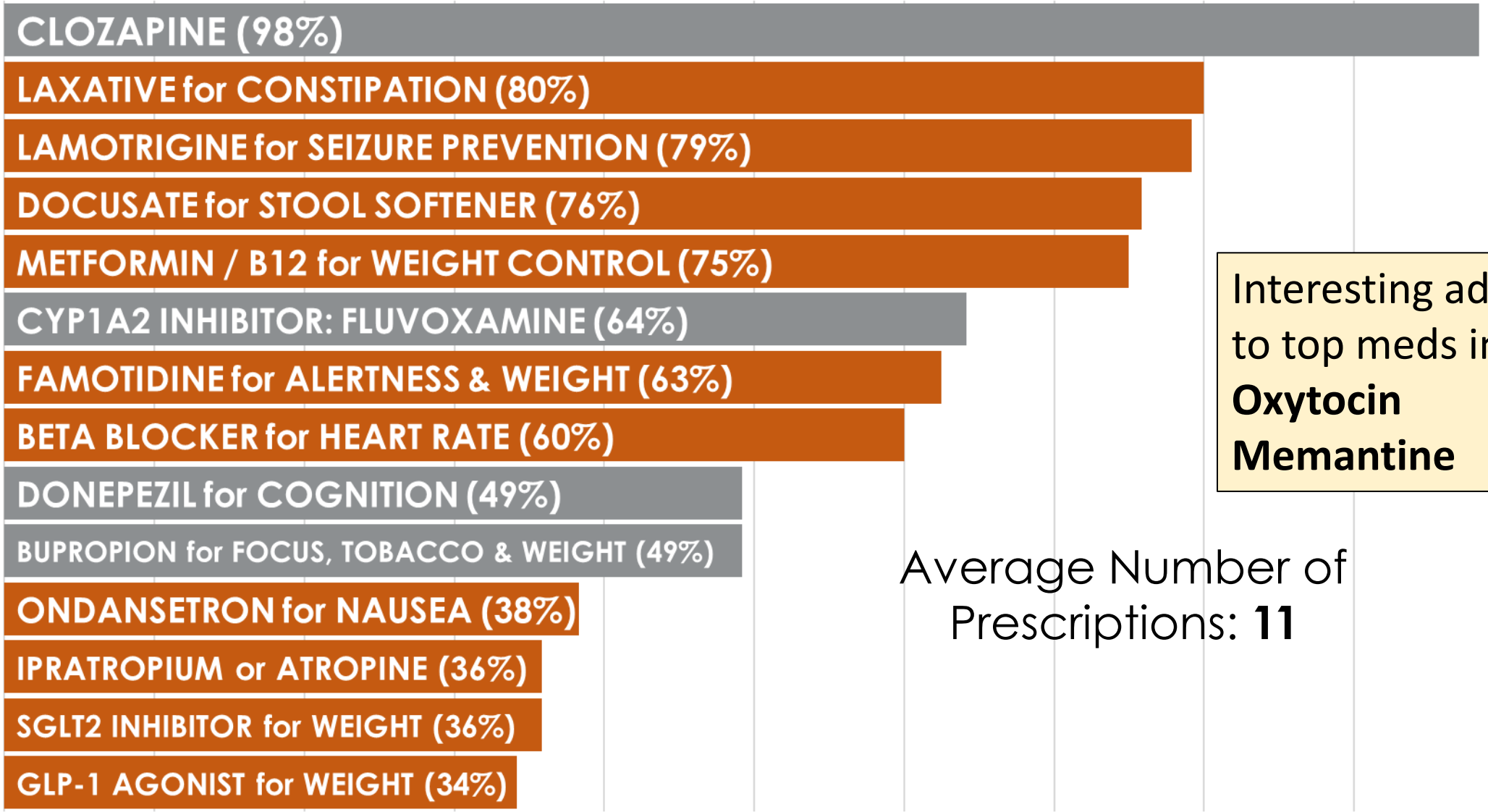
Antipsychotic Induced weight gain

Added metformin for weight control

"These medications don't do anything; they just make me fat."

Source: Team Daniel Running for Recovery

TEAM DANIEL OPTIMIZED REGIMEN (N=120)

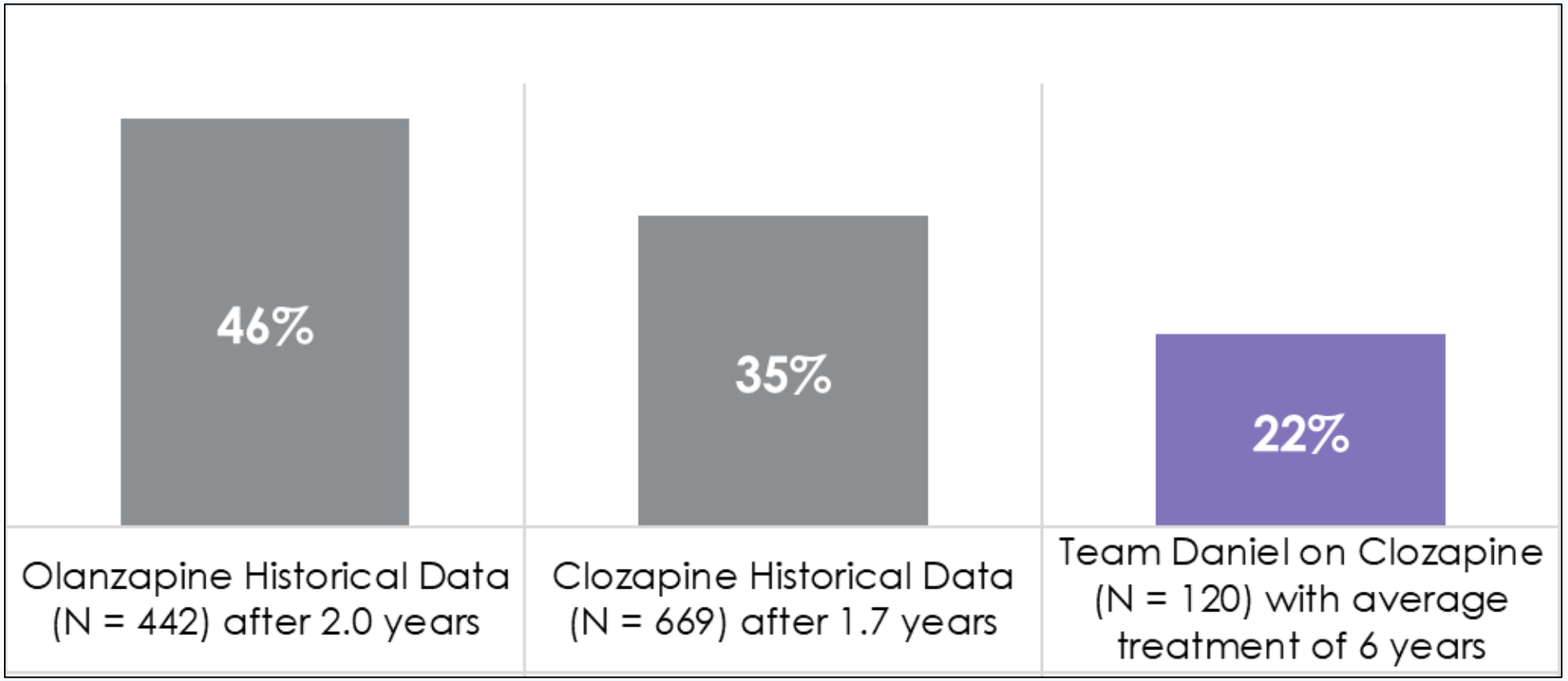


Interesting additions to top meds in 2023:
Oxytocin
Memantine

Average Number of Prescriptions: **11**

Source: Team Daniel Running for Recovery

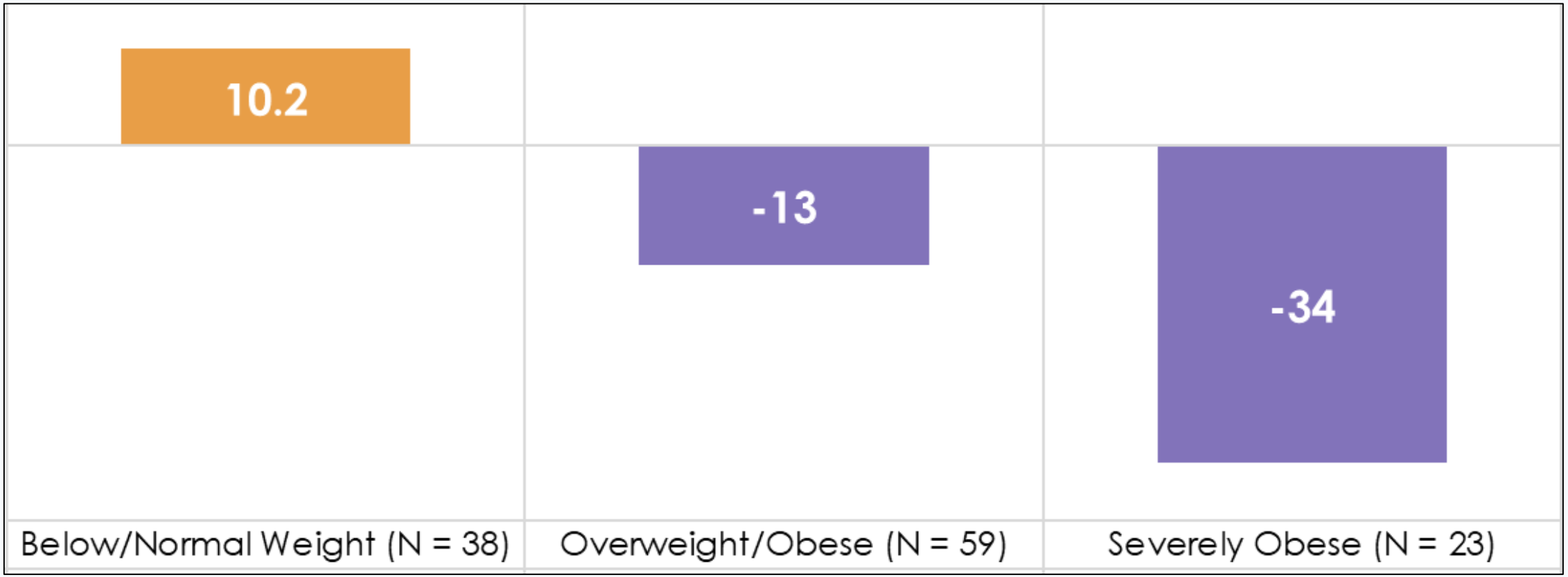
Less Weight Gain



PROPORTION OF PATIENTS WITH MORE THAN 7% INCREASE IN BODY WEIGHT

Source: Team Daniel Running for Recovery

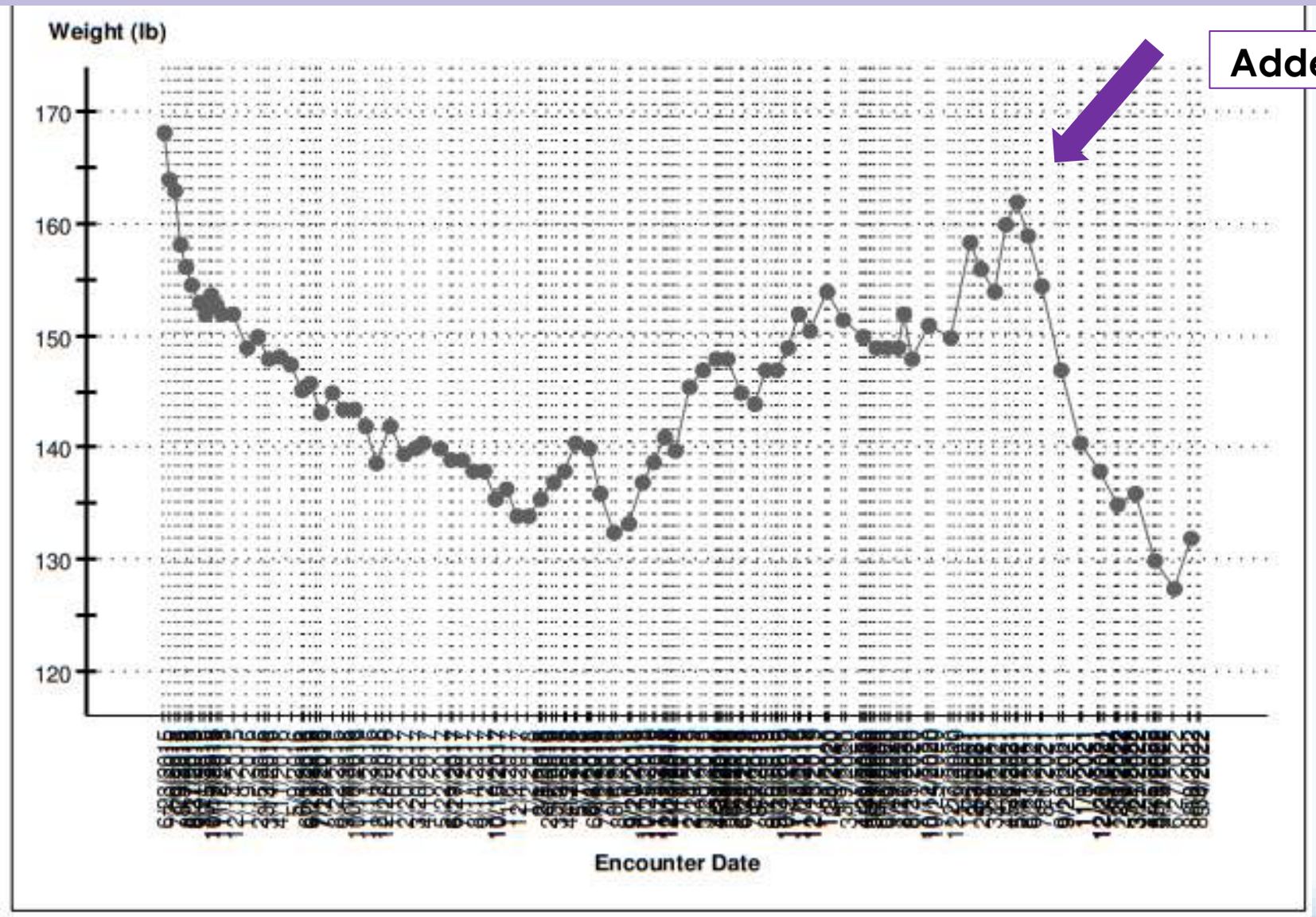
Impressive Weight Change



Team Daniel Weight Change (lb) by BMI Class at Initial Intake

Source: Team Daniel Running for Recovery

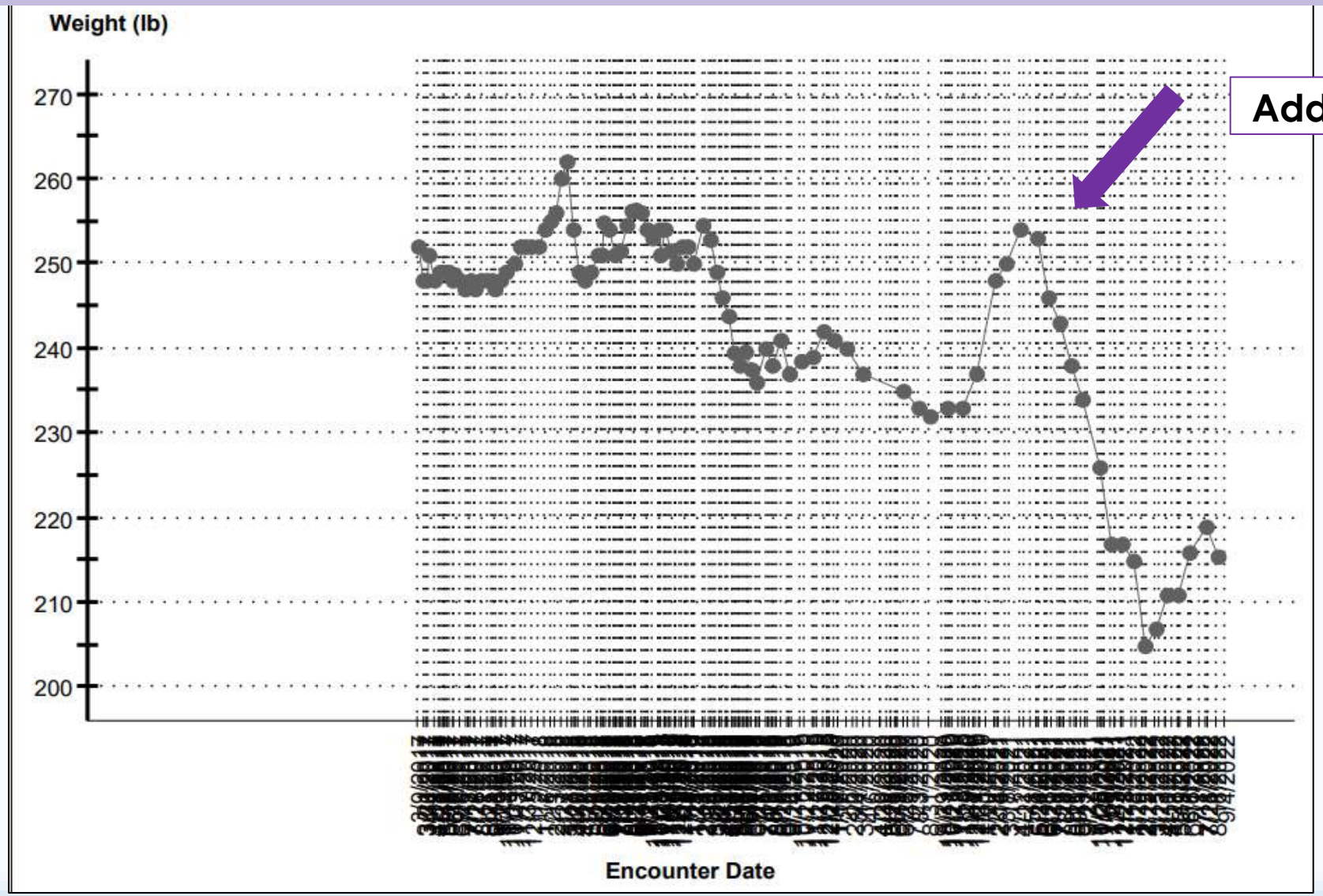
Patient Weight Over Time: GLP-1 Agonists



Female Patient

Source: Team Daniel Running for Recovery

Patient Weight Over Time: GLP-1 Agonists

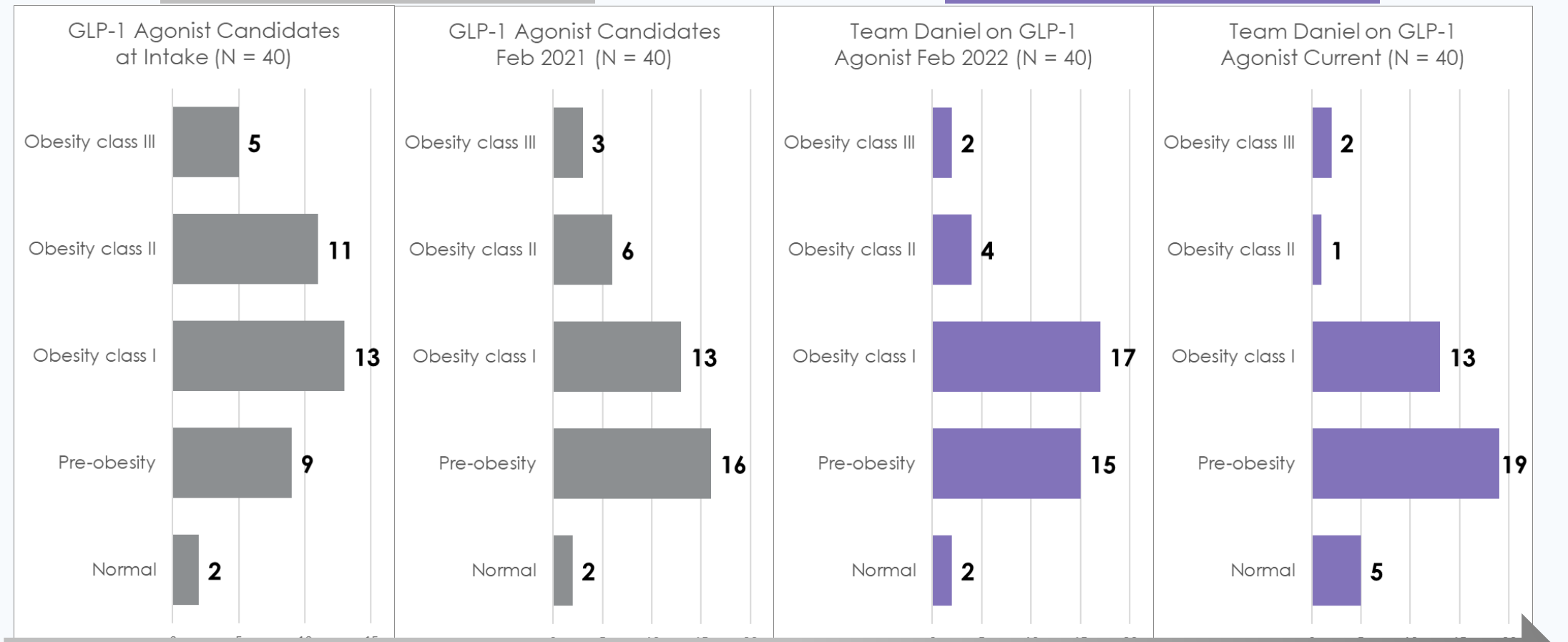


Male Patient

Source: Team Daniel Running for Recovery

Team Daniel on GLP-1 Agonist BMI Class Distribution Progress

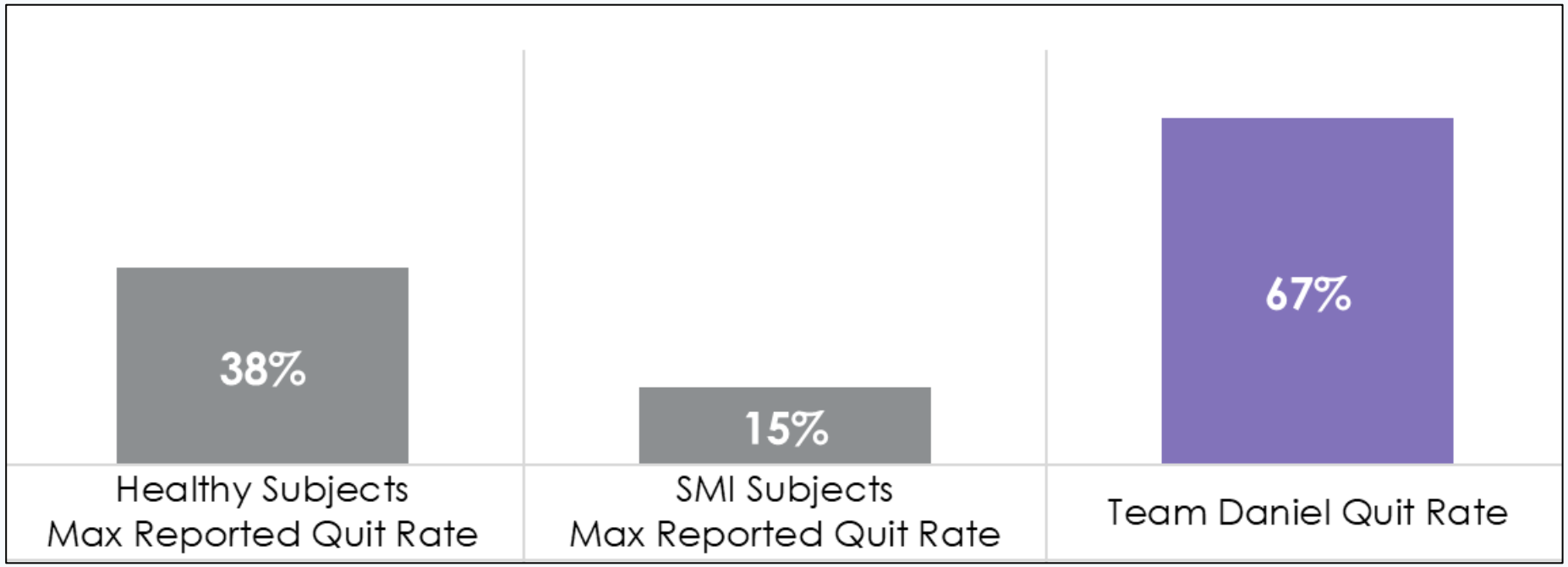
Before GLP-1 Agonist | **GLP-1 Agonist Added**



Intake	*Year 1*	*Year 2*	*Current*
73%	***55%***	***58%***	***40%***
Obese	***Obese***	***Obese***	***Obese***

Source: Team Daniel Running for Recovery

Cessation Rate Beats the Odds



31 of 46 Smokers Quit

Most used combination therapy:

87% Chantix
50% NRT
63% Bupropion

RATE OF TOBACCO CESSATION

(N=46 Team Daniel Smokers)

“Chantixphobia”

2020: Schizophrenia Subgroup of “EAGLES” Study (N = 390):

“**Varenicline** was associated with **higher abstinence rates**”

“**Did not** significantly increase the prevalence of neuropsychiatric adverse events”

2011: Adjunctive Varenicline with Antipsychotic (N = 120):

“**Some cognitive improvements** with use of adjunctive varenicline”

“Concerns regarding depression and suicidal ideation following varenicline treatment have been raised (US FDA, 2008). In our study, **no subjects showed significant depressive symptoms or suicidal ideations**.”

Evins AE et al., Efficacy and Safety of Pharmacotherapeutic Smoking Cessation Aids in Schizophrenia Spectrum Disorders: Subgroup Analysis of EAGLES (3 Nov 2020)
Shim, JC et al., Adjunctive Varenicline Treatment with Antipsychotic Medications for Cognitive Impairments in People with Schizophrenia: A Randomized Double-Blind Placebo-Controlled Trial (2 Nov 2011)

“Chantixphobia”

Nicotine-Free in 2023

*And now varenicline-free

Available as:

“Generic Varenicline”
0.5 and 1.0 mg tablets

This process takes YEARS not months.
DO NOT RUSH.
MUST manage nausea.

Name brand Chantix “pulled from the market” shortly before patent expiration

Source: Team Daniel Running for Recovery

TEAM DANIEL©

Team Daniel Clozapine Regimen Initiation Summary

Rev. 2/2/2022

		Clozapine	Initial PRN's	Colace (Constipation)	Metformin ER (Weight Control)	Lamotrigine ER (Seizure Prophylaxis)	Other Anti-psychotics	Substance Use	Smoking
MONTH 1	Week 1	12.5 mg PM	Zofran (nausea) 4 - 8 mg, up to 2X daily 1% Atropine drops sublingual (salivation) 1 - 3 drops at bedtime Up to 3 drops 3x daily Famotidine -H2 blocker (acid reflux) 20 mg 2X daily and/or omeprazole** once daily Beta Blocker i.e. propranolol (tachycardia) 10 mg up to 3X per day Use 10-20 mg PRN for anxiety Consider PRN clozapine 12.5 - 25 mg for daytime psychosis/anxiety Desmopressin (nocturnal enuresis/urinary urgency) 0.1 mg at bedtime to start Klonopin 0.5 mg 2X daily for catatonia that has not responded to therapeutic clozapine serum levels. **PPI's decrease clozapine level		Start within first month of treatment to prevent metabolic syndrome and weight gain.	Prophylactic seizure prevention for patients with seizure history, mood disorder, or clozapine serum level over 500 ng/mL. This is especially critical to establish if a patient may need fluvoxamine in the future.	Acute psychosis: temporarily consider Zyprexa, Abilify or risperidone; to be discontinued after a therapeutic clozapine level is reached.	No changes first 2-4 weeks; keep it level. Discuss dangers of marijuana/THC. Consider 50 mg naltrexone (PM) for SUD.	Smoking decreases serum levels on average 50%
	Week 2	25 mg PM							
	Week 3	50 mg PM (Start TDM)		100 mg PM					
	Week 4	75 mg PM		Customize bowel regimen per patient symptoms: - Colace up to 400 mg - Senna-S - Dulcolax - Miralax - Linzess if needed (no fiber supplements) Use Bristol Stool chart and communicate often - patients may not be forthcoming.	500 mg PM				Discuss transition to vape or ideally NRT which is preferred.
MONTH 2	Week 5	100 mg PM*			500 mg PM	25 mg AM		As clozapine becomes effective discuss life goals and how to transition from harmful substances. Consider drug counseling, DBT, possibly 12-step programs. DO NOT PUSH. Avoid short-acting benzodiazepines like Xanax. PRN Ativan or klonopin (low dose) for acute symptoms only during initial clozapine titration; discontinue after acute symptoms subside.	
	Week 6	125 mg PM*			500 AM/500 PM	25 mg AM	Slowly down-taper and discontinue sleeping pills, stimulants, ADHD medications, and all other antipsychotics: clozapine is most effective as a mono-therapy antipsychotic. Smokers will require higher doses of clozapine and a longer transition from previous medications.		
	Week 7	150 mg PM*			500 AM/500 PM	50 mg AM			
	Week 8	175 mg PM*			500 AM/1000 PM	50 mg AM			Consider Chantix or bupropion and other means of reducing dependence on nicotine. Continue to explain the value of non-smoked forms.
MONTH 3	Week 9	Increase 25 mg weekly or every two weeks per symptoms and Therapeutic Drug Monitoring (TDM). Therapeutic range begins when clozapine serum level reaches 350-500 ng/mL. Some patients need to go higher for adequate symptom control. Consider splitting dose for strong positive symptoms with 2:1 ratio bedtime to morning dose.			500 AM/1000 PM	Continue increasing lamotrigine 50 mg every two weeks up to 200 mg. If lamotrigine is not tolerated consult Dr. Laitman for the next best option: - Gabapentin - Keppra - Trileptal (check for Asian ancestry) - Topamax Depakote is NOT recommended due to increased risks / side effects. **Watch carefully for Stevens-Johnson rash.**			
	Week 10				1000 AM/1000 PM				
	Week 11				Consider Farxiga/Xigduo and Trulicity (or similar) in patients with continuing weight or metabolic concerns. Metformin depletes B12 - add 1000 mcg daily.				
	Week 12								
MONTH 4	Week 13								
	Week 14								
	Week 15								
	Week 16								

Dr. Robert Laitman mobile: 914-629-5130

*** Note: Slow clozapine titration reduces incidence of myocarditis, seizure, cardiomyopathy and pneumonia. Start TDM at 50 mg to confirm patient adherence.**

Cautions:

- **Consult Dr. Laitman for instructions on how to handle medications in previous regimen that are anticholinergic or antihistaminergic, or that may lower blood pressure, increase clozapine levels or increase seizure risk.**
- **For mild neutropenia (ANC < 1500 ug/mL or ANC < 500 ug/mL for a BEN patient) start 450mg of lithium ER (PM dose). Increase as needed to 1.2 mmol/L serum level until resolved.**
- **Indigenous/Asian/Native American descent are slow metabolizers and on average need 1/3 the dosage of European descent. Slower titration with frequent TDM is recommended.**
- **Baseline tests prior to initiating clozapine: EKG, metabolic panel, A1C, ANC, HSCRP lipid panel and where financially feasible EEG/Brain MRI.**

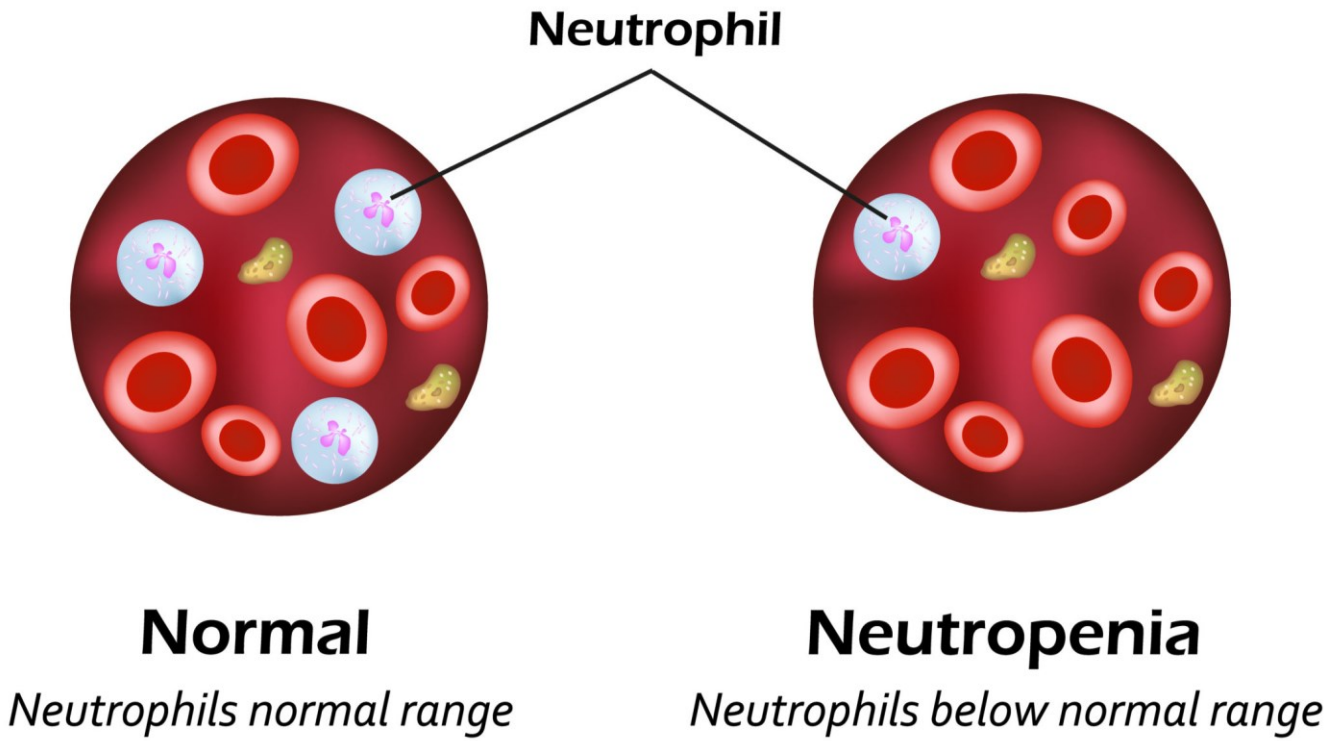
Psychiatrists Top Ranked Barriers to Clozapine

#1 Excessive Bloodwork

#2 Lack of experience / education

(Kilaria S and Kelly DL, 2019)

Agranulocytosis = Severe Neutropenia



Measure "ANC"

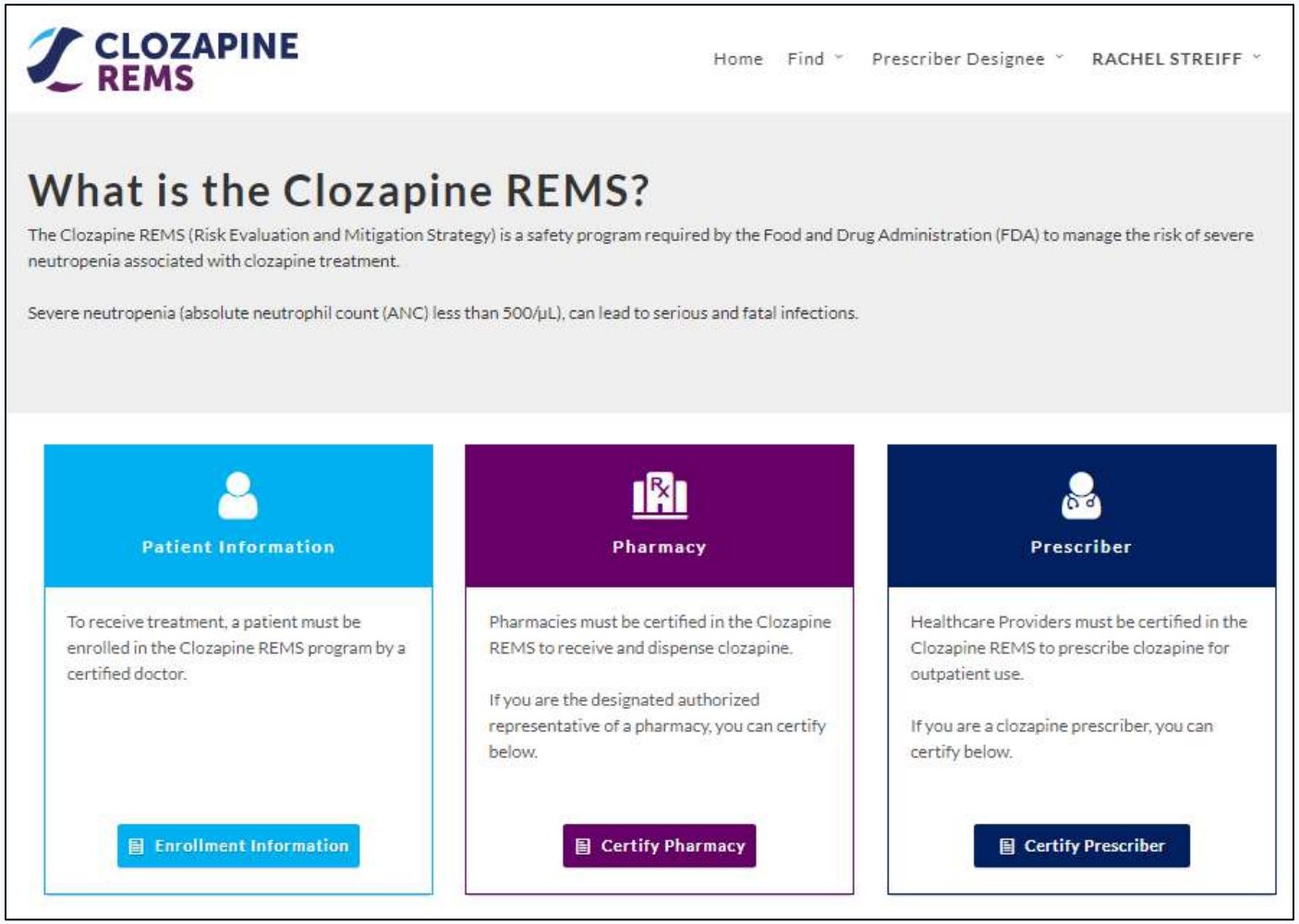
- Weekly for 6 months
- Biweekly the next 6 months
- Monthly after 1 year

A significant drop in neutrophils, or neutropenia can lead to life-threatening infections.

Source: Apollo Health Library 2021

REMS: Risk Evaluation and Mitigation Strategy

www.newclozapinerems.com



An electronic ANC surveillance platform that enables pharmacies to block clozapine refills.

Interrupting & Restarting Clozapine

Rebound psychosis within 24 hours

Catatonia and delirium

Cholinergic rebound within 48 hours

Seizures & Cardiac events

… Death

… Risk of caregiver harm

Interrupting & Restarting Clozapine

Causes:

- REMS blocking refills for errors or missing labs
- Hospitals not carrying clozapine in their formulary "because of the REMS"
- Cheeking / not cheeking
- Abrupt changes in smoking status
- Medication errors and interactions

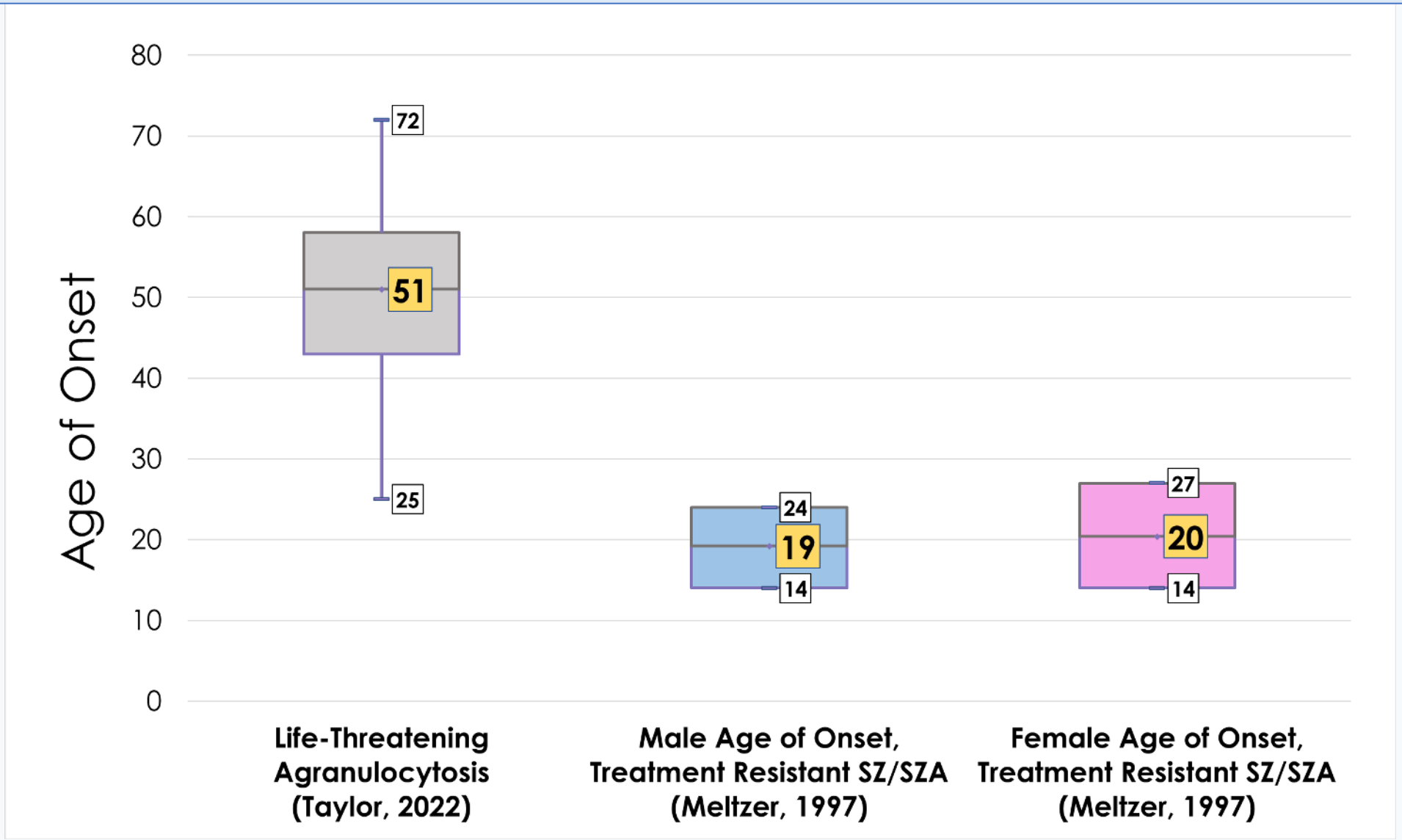
Characterization of Agranulocytosis (Taylor, 2022)

- 14-year study of 3500 patients: **0.23% risk, 0 deaths**
- Most cases are **not life-threatening**
- **May not even be clozapine-related**
- **No occurrences after 105 days**
- Almost exclusively affects **elderly, at risk patients**

Mandatory Monitoring Causes More Harm Than Good.

Taylor, D et al. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* **8**, 21 (2022).

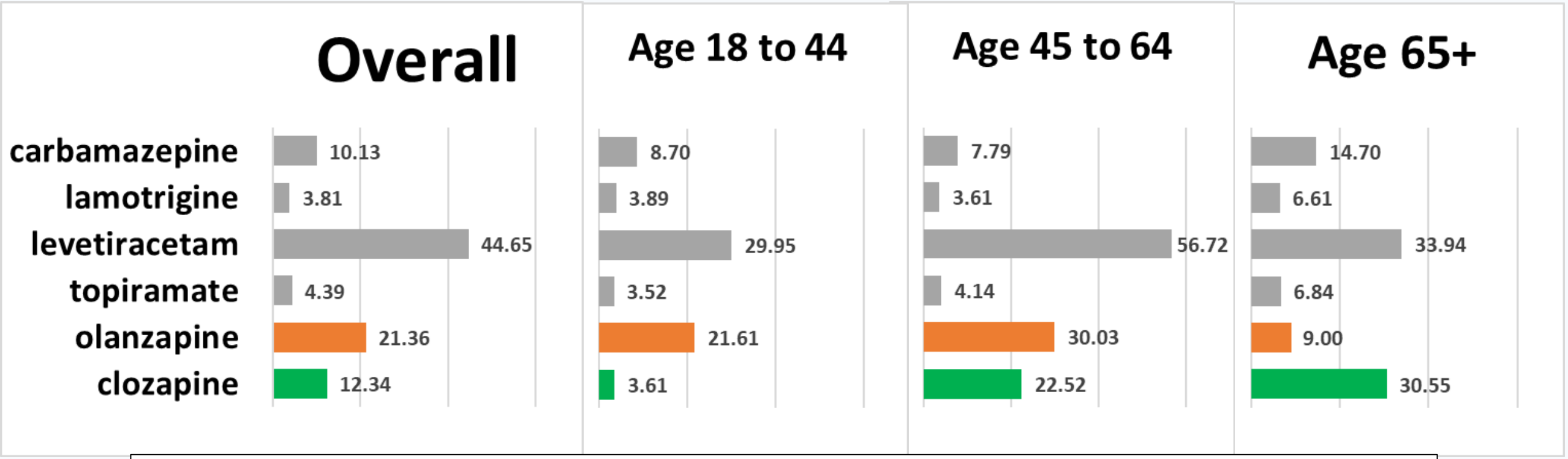
Life-Threatening Agranulocytosis: Age Effect



Meltzer HY, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry*. 1997 Apr;154(4):475-82.
Taylor, D et al. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* **8**, 21 (2022).

FDA's Mini-Sentinel Distributed Database: Results

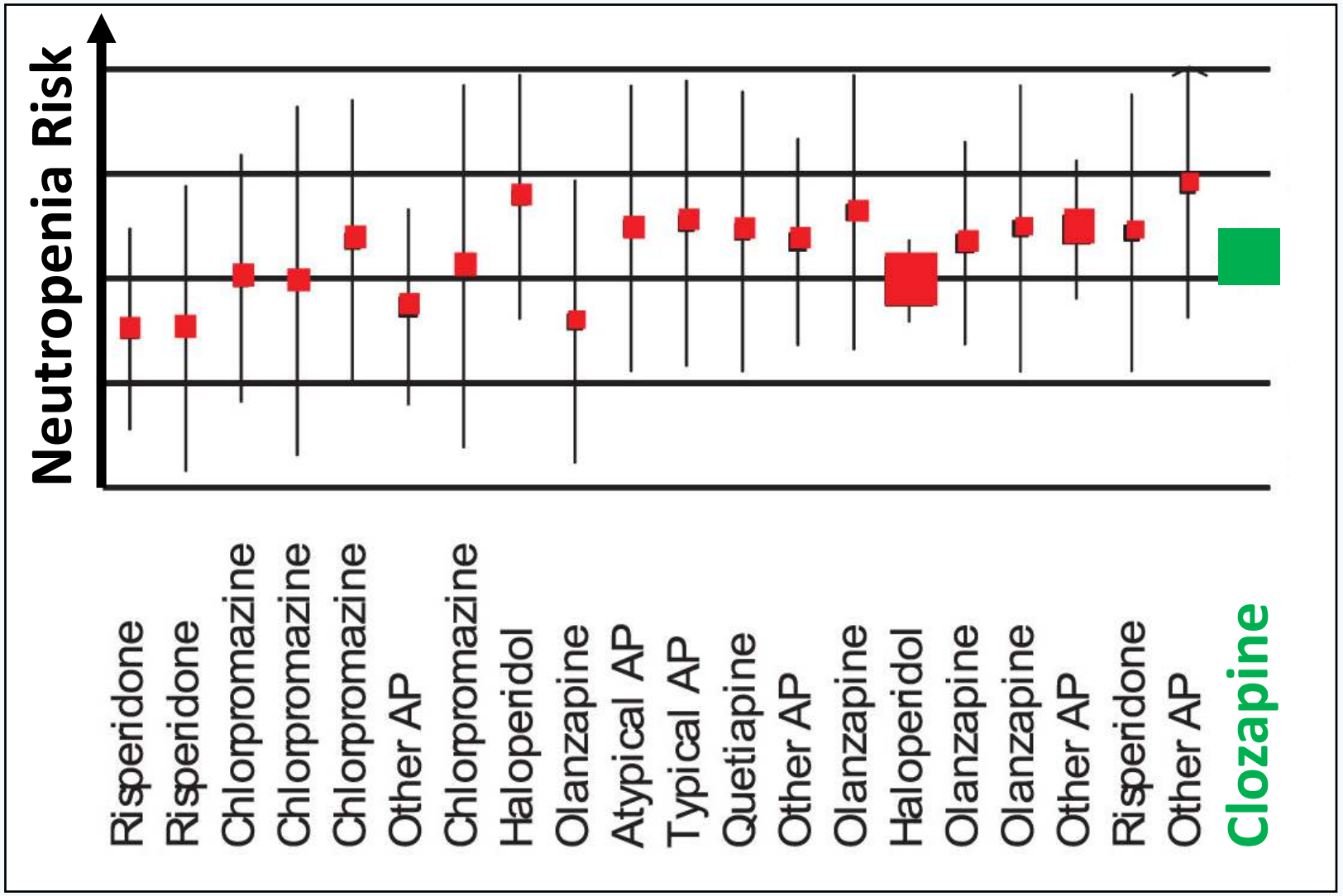
Neutropenia Events /10k Years at Risk in 90M CMS subscribers (2000 – 2013)



In the age group 18 to 44 the incidence is FIVE TIMES HIGHER for olanzapine than clozapine

FDA Sentinel Initiative. "Diagnosis of Agranulocytosis Following New Use of Anti-epileptic Drugs, Clozapine, and Olanzapine." Mini-Sentinel Distributed Database (MSDD) March 21, 2018 link: MS_Brief_Report_1_to09y05_mpr_wp26_v01.pdf (sentinelinitiative.org)

Clozapine: Similar Risks to Other Antipsychotics



Myles, 2019:

Meta-Analysis of 20 studies; over 2,800 patients.

Clozapine does **not** have a stronger association with neutropenia than other antipsychotic medications.

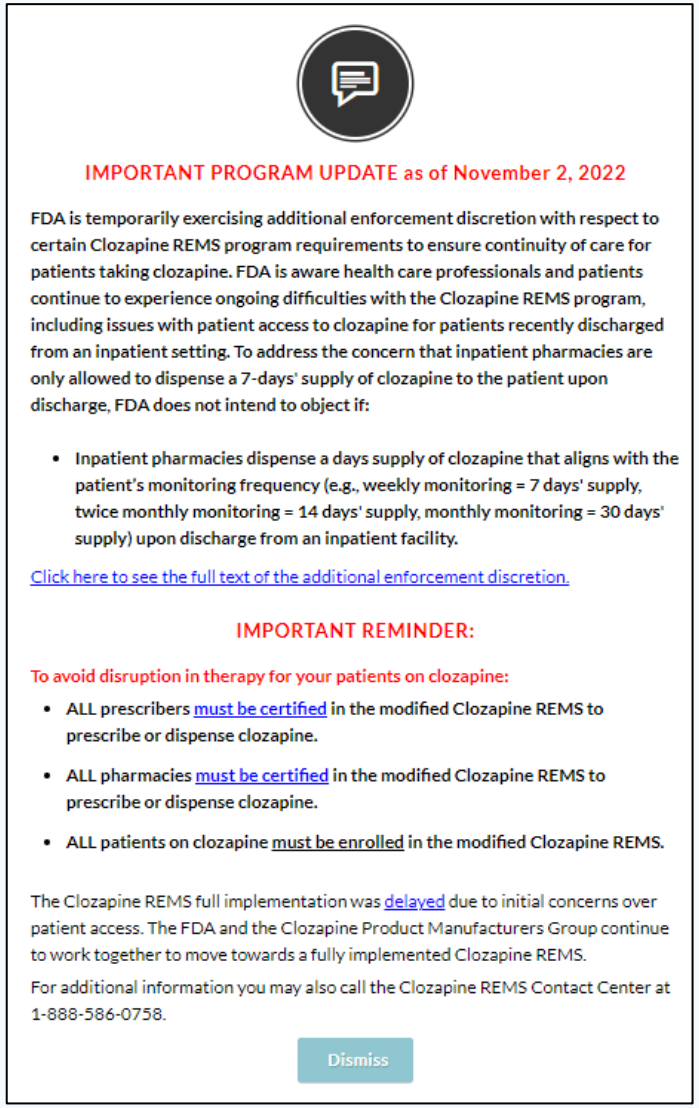
Monitoring isolated to clozapine is not justified.

Myles N, et al. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Australian & New Zealand Journal of Psychiatry*. 2019;53(5):403-412

Discrimination Against TRS

Medication	Indication / Use	Incidence of Severe Neutropenia	Neutrophil Monitoring Guidelines	REMS for ANC?
Palbociclib **Ribociclib**	Advanced or metastatic breast cancer	Severe: 10% (Overall 80%)	Biweekly, first 2 months Monthly or "as clinically indicated" thereafter	**NO**
Sulfasalazine	Ulcerative colitis, rheumatoid arthritis	3%	Biweekly, first 3 months Monthly the next 3 months Quarterly thereafter	**NO**
Procainamide	Anti-arrhythmic	0.5% (20 – 25% mortality)	Weekly, first 3 months "Periodically" thereafter	**NO**
Carbamazepine	Anticonvulsant	Severe: 0.5% 2.1%	"If patient exhibits…decreased WBC or platelet counts…monitor closely"	**NO**
Propylthiouracil	Hyperthyroidism	0.2 – 0.5%	Test if symptoms appear, "such as fever or sore throat."	**NO**
Olanzapine	Antipsychotic	True incidence unknown	"Patients with [clinically significant] history should [be] monitored frequently during the first few months of therapy"	**NO**
Clozapine	**Antipsychotic**	**0.23%**	**Weekly first 6 months** **Biweekly next 6 months** **Monthly forever**	**YES**

REMS: Risk Evaluation and Mitigation Strategy



IMPORTANT PROGRAM UPDATE as of November 2, 2022

FDA is temporarily exercising additional enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine. FDA is aware health care professionals and patients continue to experience ongoing difficulties with the Clozapine REMS program, including issues with patient access to clozapine for patients recently discharged from an inpatient setting. To address the concern that inpatient pharmacies are only allowed to dispense a 7-days' supply of clozapine to the patient upon discharge, FDA does not intend to object if:

- Inpatient pharmacies dispense a days supply of clozapine that aligns with the patient's monitoring frequency (e.g., weekly monitoring = 7 days' supply, twice monthly monitoring = 14 days' supply, monthly monitoring = 30 days' supply) upon discharge from an inpatient facility.

Click here to see the full text of the additional enforcement discretion.

IMPORTANT REMINDER:

To avoid disruption in therapy for your patients on clozapine:

- ALL prescribers must be certified in the modified Clozapine REMS to prescribe or dispense clozapine.
- ALL pharmacies must be certified in the modified Clozapine REMS to prescribe or dispense clozapine.
- ALL patients on clozapine must be enrolled in the modified Clozapine REMS.

The Clozapine REMS full implementation was delayed due to initial concerns over patient access. The FDA and the Clozapine Product Manufacturers Group continue to work together to move towards a fully implemented Clozapine REMS.

For additional information you may also call the Clozapine REMS Contact Center at 1-888-586-0758.

Dismiss

The REMS program is currently "suspended" following a dangerous system conversion in 2021 that blocked thousands of scripts.

This annoying pop-up appears twice to state:

"The FDA is temporarily exercising additional enforcement discretion"

This has been widely misinterpreted as MORE restrictive, not LESS, and has caused even greater patient harm.

Causes of Low Neutrophils

Normal Range 1,500 to 6,000 cells/uL	**Our observation: Patients are more likely to be stopped or interrupted with tragic consequences than the testing is likely to prevent agranulocytosis.**
1,500 cells/uL Mild Neutropenia	• Mild illness • Normal variation • OTC medications (antacids, arthritis cream) • Being sedentary / asleep • **Being Black**
500 cells/uL Severe Neutropenia	• Lab or data entry error • Cancer treatments • Other illnesses or medications • **Clozapine-induced agranulocytosis**

A Top Cause of Blocked Refills: Data Entry Error

TEST	RESULTS	REFERENCE RANGES	UNITS
HEMATOLOGY			
CBC w/ Differential, w/ Platelet			
WBC	4.8	4.0 - 10.5	k/mm3
RBC	4.27	4.20 - 5.60	m/mm3
Hemoglobin	13.6	12.0 - 15.0	g/dL
Hematocrit	42.9	35.0 - 45.0	%
MCV	**100.5 H**	78.0 - 95.0	fL
MCH	31.9	26.0 - 32.0	pg
MCHC	31.7	31.0 - 37.0	g/dL
Platelet Count	288	130 - 450	k/mm3
RDW(sd)	47.8	38.0 - 49.0	fL
RDW(cv)	13.0	11.0 - 15.0	%
MPV	10.6	7.5 - 14.0	fL
Segmented Neutrophils	58.6*		%
Lymphocytes	30.0		%
Monocytes	9.4		%
Eosinophils	1.0		%
Basophils	0.8		%
Absolute Neutrophil	2.79	1.60 - 9.30	k/uL
Absolute Lymphocyte	1.43	0.60 - 5.50	k/uL
Absolute Monocyte	0.45	0.10 - 1.60	k/uL
Absolute Eosinophil	0.05	0.00 - 0.70	k/uL
Absolute Basophil	0.04	0.00 - 0.20	k/uL
Immature Granulocytes	0.2		%
Absolute Immature Granulocytes	0.01	0.00 - 0.10	k/uL
NRBC RE, Nucleated Red Blood Cell Percent	0.0	0.0 - 1.0	%

*Segmented Neutrophils: Automated Diff

Pharmacist entered the data as 2.79 instead of 2790 causing an automatic block of the prescription refill.

This happens ALL THE TIME, especially when pharmacists ask for proof of labs.

Caregivers Speak Out Against TRS Discrimination

www.theangrymoms.com

Blood Tests Can Be Waived!

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

[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.

Prescriber Signature: **Date** (MM/DD/YYYY):

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) **(Prescriber Signature required below)**

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) ***or*** *severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia).* check **and sign below**:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.
Until (MM/DD/YYYY) _____ (not to exceed 6 months)

Prescriber Signature: **Date** (MM/DD/YYYY):

The Blood Tests are NOT a "Federal Mandate"

Source: Clozapine REMS Patient Status Form

Prescribers can waive missing labs and/or continue clozapine treatment with low ANC by selecting any of three available options on the Patient Status Form.

Blood Tests Can Be Waived!

People NEWS ENTERTAINMENT ROYALS LIFESTYLE STYLEWATCH SHOPPING

Schizophrenia Caused Eric Smith to Threaten His Mother's Life, but He Refused to Get Help — Here's Why

Like more than half of people with serious mental illness, Smith suffered from anosognosia, a condition where your brain doesn't recognize it's sick

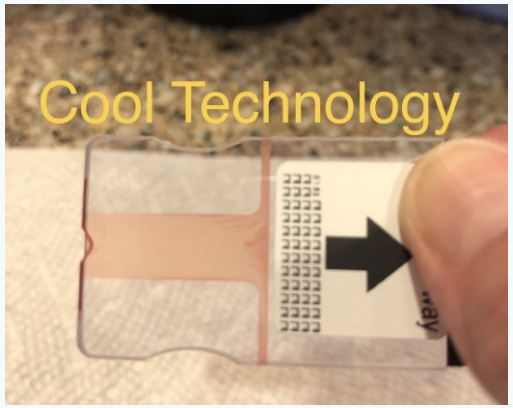
By **Eileen Finan** and **Alexandra Rockey Fleming** | Published on February 15, 2023 09:45 AM

Clozapine advocate Eric Smith has an agreement between his doctor, pharmacy, and the REMS to get bloodwork every 3 months.

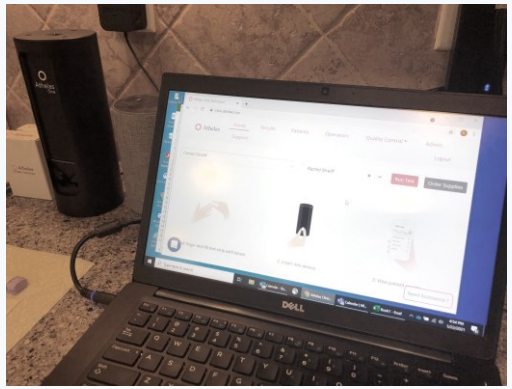
Eric has been on clozapine for over 10 years.

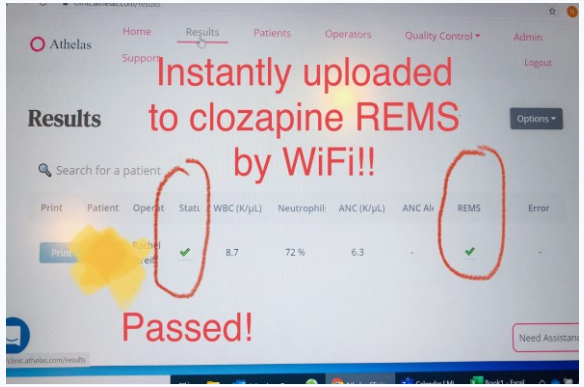
The Most Significant Innovation in the Last 10 Years

Point-of-Care Measurement of ANC for Clozapine Patients



Finger Prick Testing Real Photos from a Very Excited Patient!

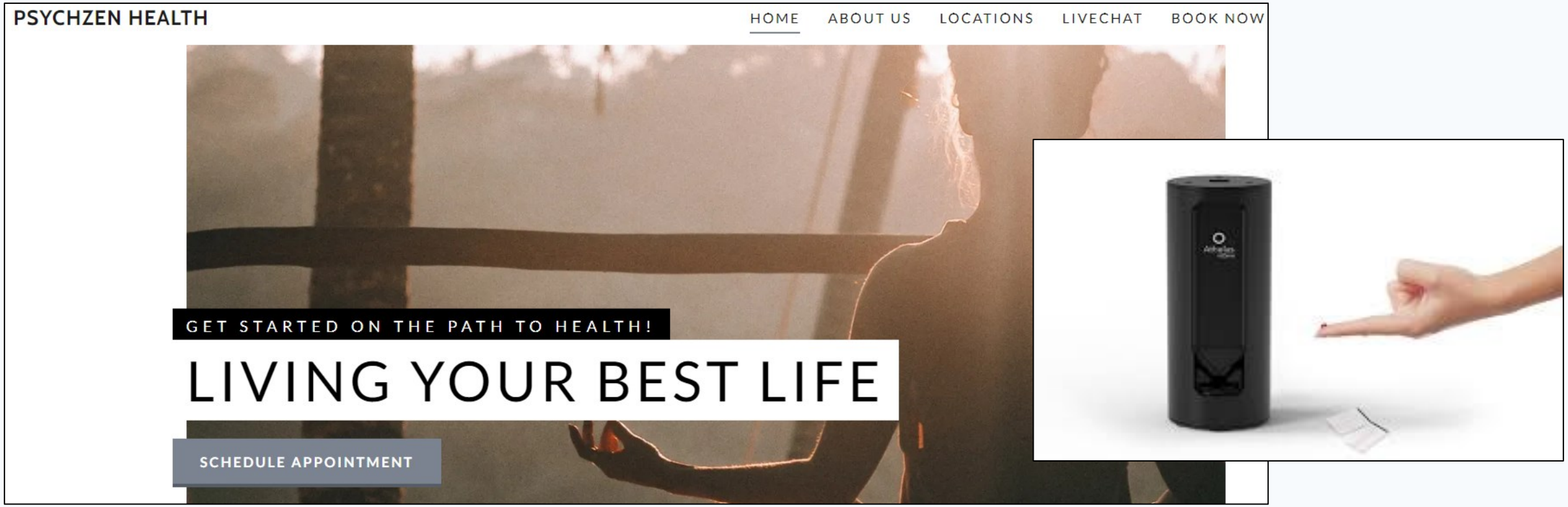




Athelas

We need to deploy this in all psychiatric hospitals, clinics and pharmacies.

The Most Significant Innovation in the Last 10 Years



Finger prick ANC is completed at every intake alongside standard vitals.

Athelas for “Home”

How does it work?

The **Athelas Home** delivers lab-quality test results in a matter of minutes with just a few drops of blood, all from the comfort of your living room.

The **Athelas Home** then signals Golden Gate Pharmacy to deliver your approved, Clozaril prescription, right to your door.

It’s as simple as that.
No travel. No needles. Just results.

Ready to get started?
Visit https://ggprx.com/clozaril/ to complete the application, find out if you are eligible and explore the details of the program.

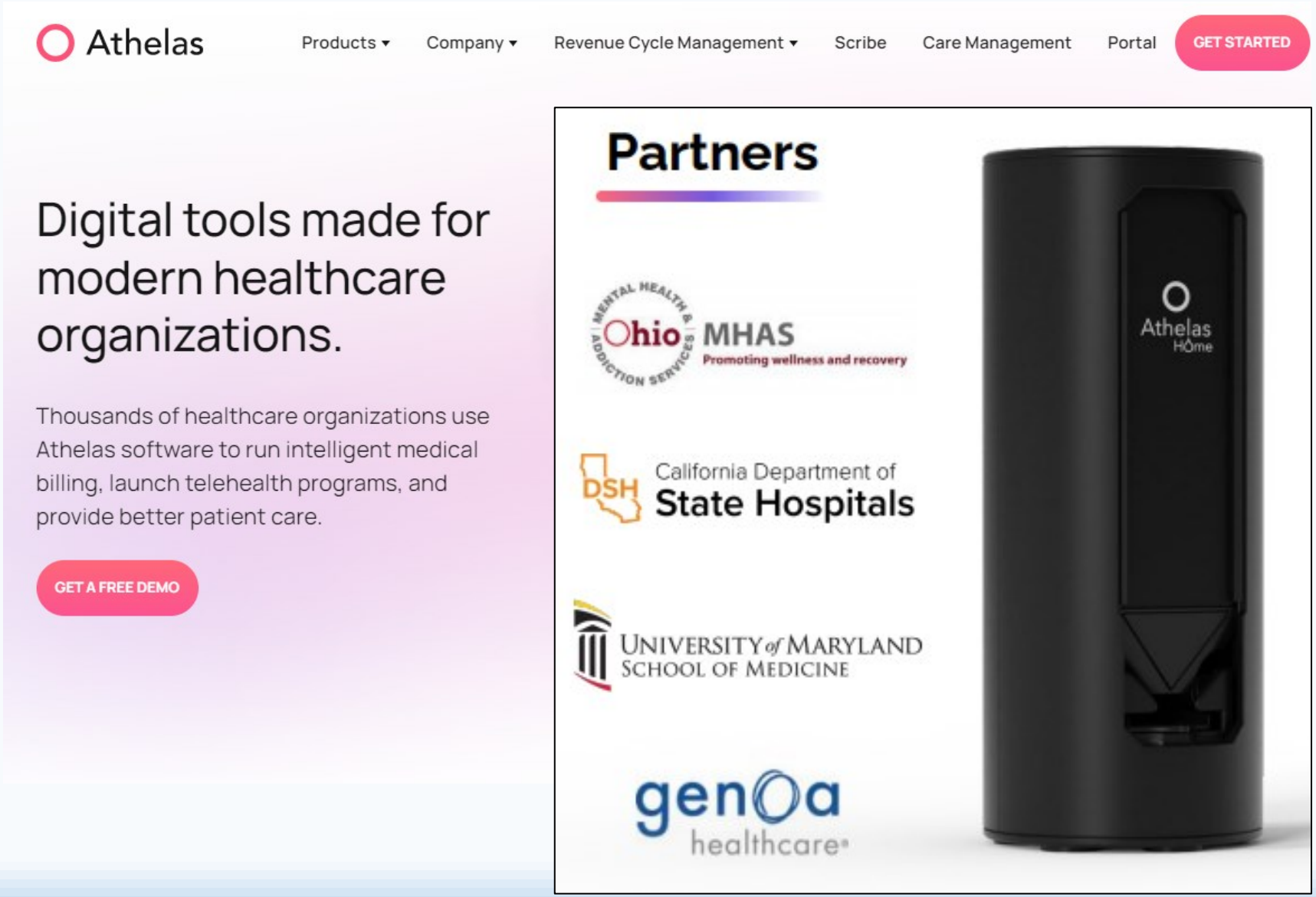
Ask your doctor if Athelas Home is right for you

GOLDEN GATE PHARMACY SERVICES Athelas

Your Home Pharmacy
Generic Clozapine
$1500 Device **$30 Test Strips**
Golden Gate Mail Order Rx
Generic Clozapine
$1000 Device **$10 Test Strips**
Golden Gate Mail Order Rx
Name Brand Clozaril®
$500 Device **$10 Test Strips**

www.ggprx.com/clozaril

Athelas for Clinics & Pharmacies



Click the "Get Started" button at **www.athelas.com**

Cost is driven by software requirements; determined by expected number of users.

Billing for a 15 min visit is how many clinics are recouping costs.

REMS: Risk Evaluation and Mitigation Strategy

Genoa Pharmacies in Phoenix Area with Athelas Devices:	City	Current Status
Partners in Recovery	Phoenix	Last test July 2022
Lifewell Behavioral Wellness (Baseline)	Phoenix	35 tests / month
Lifewell Behavioral Wellness (North)	Phoenix	60 tests / month
Lifewell Behavioral Wellness (Oak)	Phoenix	50 tests / month
Southwest Network (Osborn)	Phoenix	unknown
Southwest Network (Royal Palm)	Phoenix	unknown
Southwest Network (95th Ave)	Phoenix	unknown
Southwest Network (Bell Road)	Phoenix	unknown
Southwest Network (San Tan)	Chandler	unknown
Other Arizona Genoa Pharmacy Locations with Athelas Devices:		
COPE Community Services, Inc. (Castro) - Tucson		
Wellbeing Institute (1st Ave) - Tucson		
La Frontera (Pennsylvania St.) - Tucson		
Mohave Mental (Airway Ave.) - Kingman		
Change Point Integrated Health (White Mtn Rd.) - Show Low		
Private Practice Athelas Devices in Arizona (Currently Active):		
Serenity Mental Health - Dr. Teejay Tripp - 2355 E CAMELBACK RD PHOENIX 85106		
RI International - Tracy Crews - 11361 N 99th Ave #402, Peoria, AZ 85345		
Resilient Health Gilbert - Dr. Annees Moonjelly - 3271 E Queen Creek Rd Gilbert 85297		
Psych ZenHealth - Josiah Nwaokwa - 1095 East Indian School Rd #700, Phoenix, Arizona 85014		

Athelas devices in Arizona

FDA approved and CLIA waived

The Business Case For Clozapine

- Hospitalization: $1,000 to $4,000 PER DAY
- Direct and indirect costs of schizophrenia : $92,000 per person per year

- A study of 14,000 veterans with TRS:
  - Clozapine saves $22,000 per patient per year
  - Clozapine eliminated 18 hospitalization days per person per year

- A long-term study of 171 patients showed clozapine reduced hospitalizations from 6 per year to <1 per year.

Beyond the cost effectiveness; we must end suffering

#2 Barrier after REMS: Lack of Provider Education

Model: A large Medicaid Managed Care Plan in New York

Continuing Medical Education (CME)

- Launching 3-part CME series in June 2023 on optimal use of clozapine for TRS.
- Target audience:
  - Network psychiatrists (inpatient & outpatient)
  - Network psych nurse practitioners
  - Residents / fellows
  - Pharmacists specializing in psychiatry

We must train and support prescribers!

We MUST Compensate for the Added Work

Model: A large Medicaid Managed Care Plan in New York

Exploring opportunities to develop and trial a Case Rate for Clozapine

- First 6 months will be higher compensation
- Ongoing case reimbursement will encourage adherence & patient support
- Cost will cover:
  - Care management & coordination
  - Medical management

Note: NY Office of Mental Health (OMH) "flags" individuals who may benefit from clozapine; they will be using this data to initiate clozapine trials.

- **Large numbers NOT receiving clozapine is prompting this change!**

We must train and support prescribers!

We MUST Compensate for the Added Work

Example: Local nurse practitioner in Phoenix, AZ

CMS compensation for clozapine visit:

$99 to $109

- Difficult patients
- Numerous prescriptions (average = 11)
- Weekly lab orders
- REMS Entry
- Family partnership & communication
- Hospitalizations w/doc-to-docs
- Numerous adverse effects to monitor

CMS compensation for Spravato® visit:

$150 to $178

- Cooperative patients
- REMS entry of easy vital signs
- Easy monitoring (rest in a chair)

Twice weekly first month
Weekly second month
Weekly / biweekly thereafter

We must train and support prescribers!

Summary of Innovations in Clozapine Therapy

- Ultra-slow titration (aka “Micro-dosing Approach”)
  - Nearly eliminates side effects
  - The “Team Daniel” practice reports 94% rate of continuance
- Use of rational polypharmacy to treat the whole patient
  - Advocates call this “The Laitman Protocol” or “Meaningful Recovery Protocol”
  - Focus on prevention (seizures, bowel obstruction, weight gain, pneumonia)
  - Most prescriptions are NOT psychiatric, a **medical** approach is needed
- About 25% need higher serum levels than the traditional boundaries
  - Requires anticonvulsant meds and frequent serum level measurements

Summary of Innovations in Clozapine Therapy

- Athelas finger-prick devices are reasonable disability accommodations
  - Start using them! Discounts available!
  - Insurers/payors need to start covering this vital technology
- Start waiving labs, do NOT let patients run out of medication
- Chantix (varenicline) works, start using it!
- Consider clozapine with cannabis-use disorder
- We must end the clozapine REMS
- We must use science to guide neutropenia monitoring

Questions?