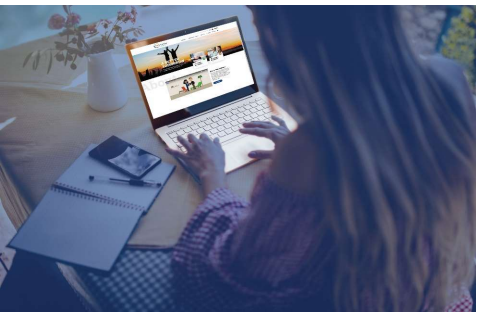
WELCOME

Clozapine & LAI Virtual Forum

September 7, 2022 | 4:00 – 4:45 pm ET



The Clozapine & LAI Virtual Forum is a peer-to-peer, interactive dialogue between psychiatrists, nurse practitioners, and other prescribing clinicians.
It is informal, no registration required — just join our Zoom call and share your challenges and questions on the month's trending topic around either clozapine or LAIs.

TODAY'S TOPIC:

Appropriate Use of Weight Loss Medication with Clozapine with a Focus on GLP-1 Agonists

MODERATORS

Donna Rolin, PhD, APRN

SMI Adviser Nursing Expert; University of Texas, Austin

Dr. Donna Rolin is Clinical Associate Professor and the Director of the Psychiatric Mental Health Nurse Practitioner program at the University of Texas with 23 years of experience in psychiatric nursing, including inpatient, community, forensic, and older adult settings.

Robert Cotes, MD

SMI Adviser Physician Expert; Emory University

Dr. Robert Cotes, MD, is an Associate Professor at Emory University School of Medicine in the Department of Psychiatry and Behavioral Sciences. He has interest in clozapine, characterizing persistent symptoms of schizophrenia, understanding cardiometabolic side effects of antipsychotic medications, and first episode psychosis.

Robert Laitman, MD

Clozapine Expert

Dr. Robert Laitman is an internist who specializes in the use of clozapine in an optimal fashion for individuals with schizophrenia or other psychotic spectrum disorders. He serves on the Board of Directors for the Schizophrenia and Related Disorders Alliance of America and is also a board member of the Westchester chapter of the National Alliance of Mental Illness. Dr. Laitman and his wife started Team Daniel, a 501 c-3 non-profit, to advocate for and support people living with mental illness.

Discussion Questions for Virtual Forum:
Appropriate Use of Weight Loss Medication with Clozapine with a Focus on GLP-1 Agonists

- Do any insurances cover GLP-1 meds for clozapine or other SGAs?
- What medications or alternatives can I prescribe to promote weight loss to patients on clozapine?
- What screening panel blood tests must be used on a standard basis besides WBC to identify and address metabolic effects early and monitor continuously if Clozapine is working well overall?

Robert Laitman, M.D. *of*

TEAM DANIEL

presents

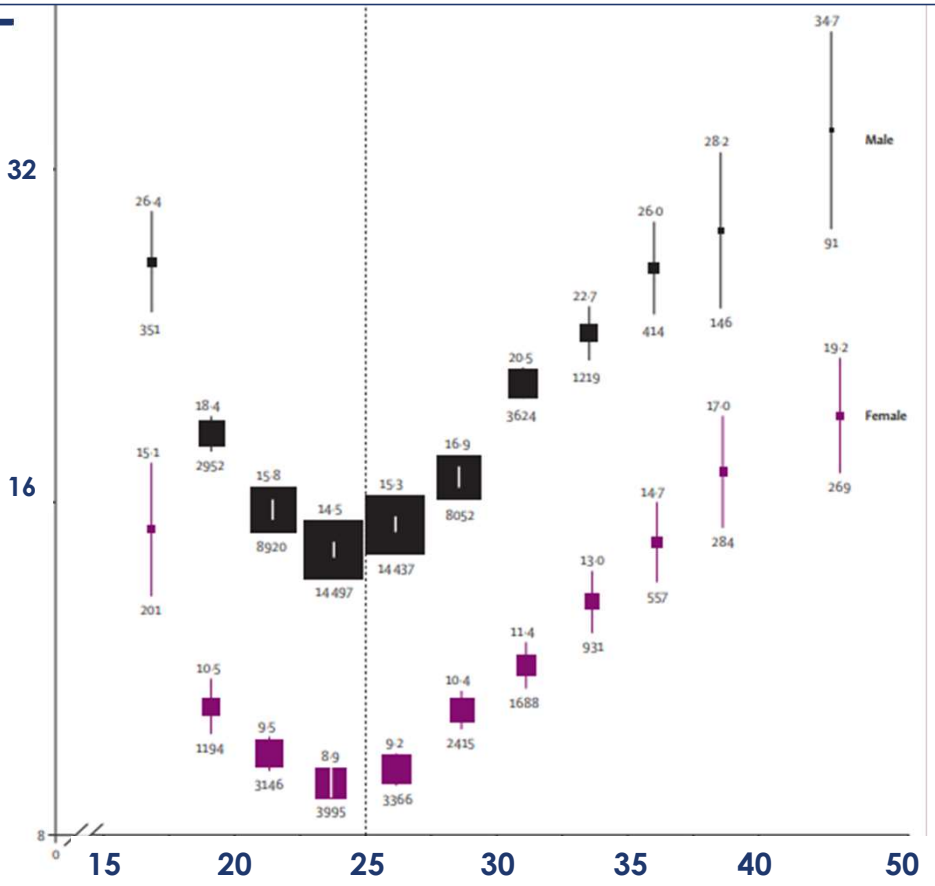
Appropriate Use of Weight Loss Medication with Clozapine with a Focus on GLP-1 Agonists

TEAM DANIEL
Running for Recovery
from Mental Illness

Sept. 7, 2022

All-Cause Mortality Versus BMI for Each Sex in the Range 15–50 kg/m2

(excluding the first 5 years of follow-up)



Relative risks at ages 35–89 years, adjusted for age at risk, smoking, and study, were multiplied by a common factor (ie, floated) to make the weighted average match the PSC mortality rate at ages 35–79 years.

Floated mortality rates shown above each square and numbers of deaths below.

Area of square is inversely proportional to the variance of the log risk.

Boundaries of BMI groups are indicated by tick marks.

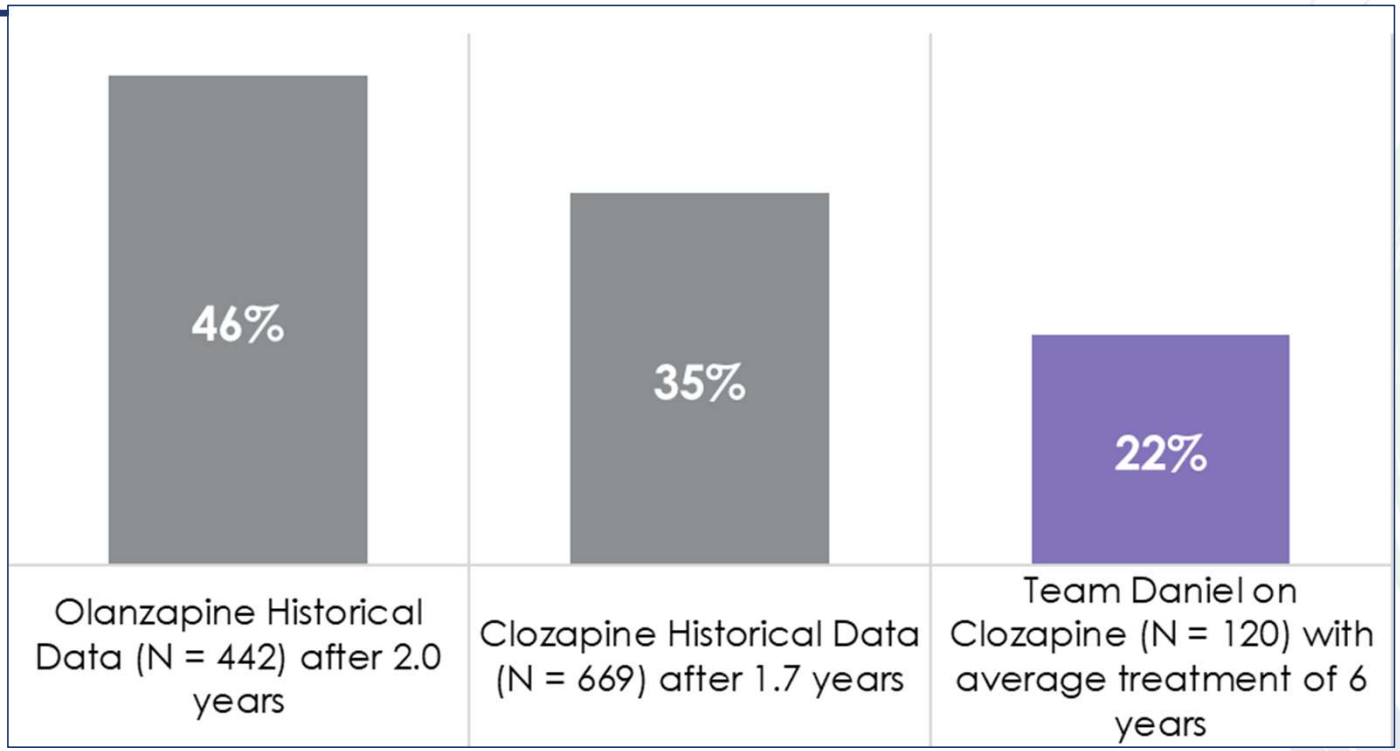
95% CI's for floated rates reflect uncertainty in the log risk for each single rate.

Dotted vertical line indicates 25 kg/m^2 (boundary between upper and lower BMI ranges in this report).

Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies.

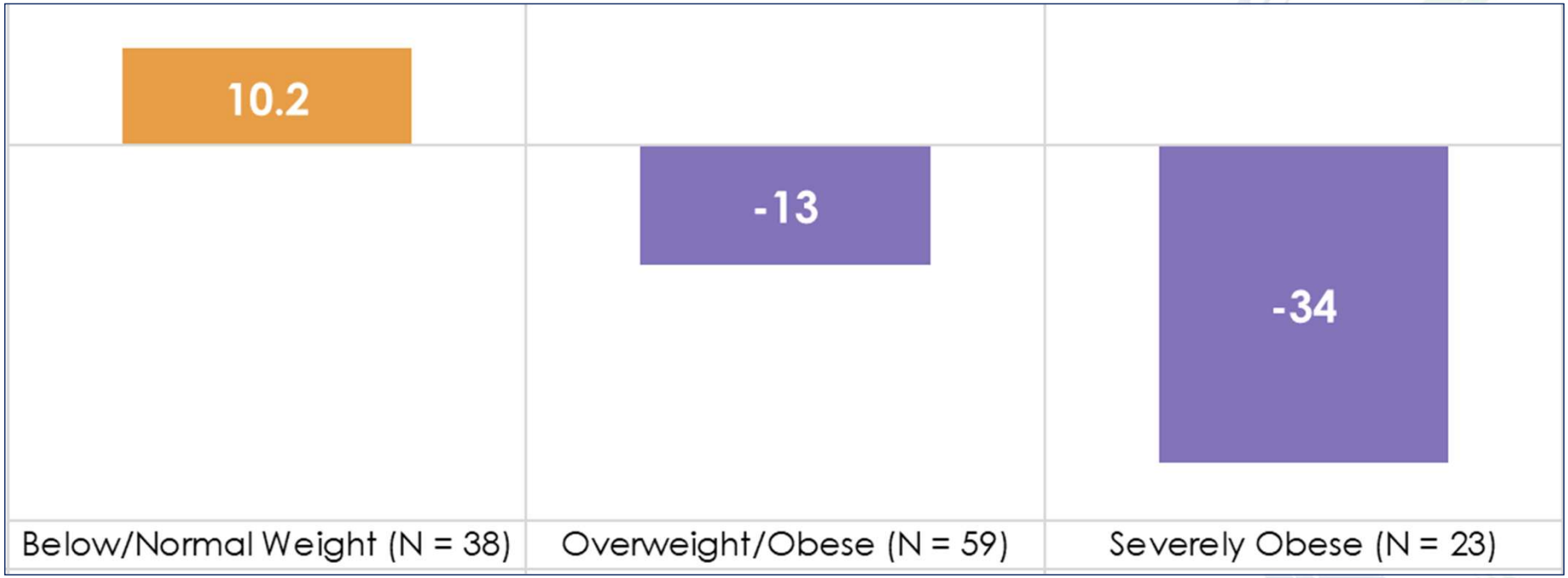
Lancet. 2009 Mar 28;373(9669):1083-96. doi: 10.1016/S0140-6736(09)60318-4. Epub 2009 Mar 18. PMID: 19299006; PMCID: PMC2662372.

Less Weight Gain



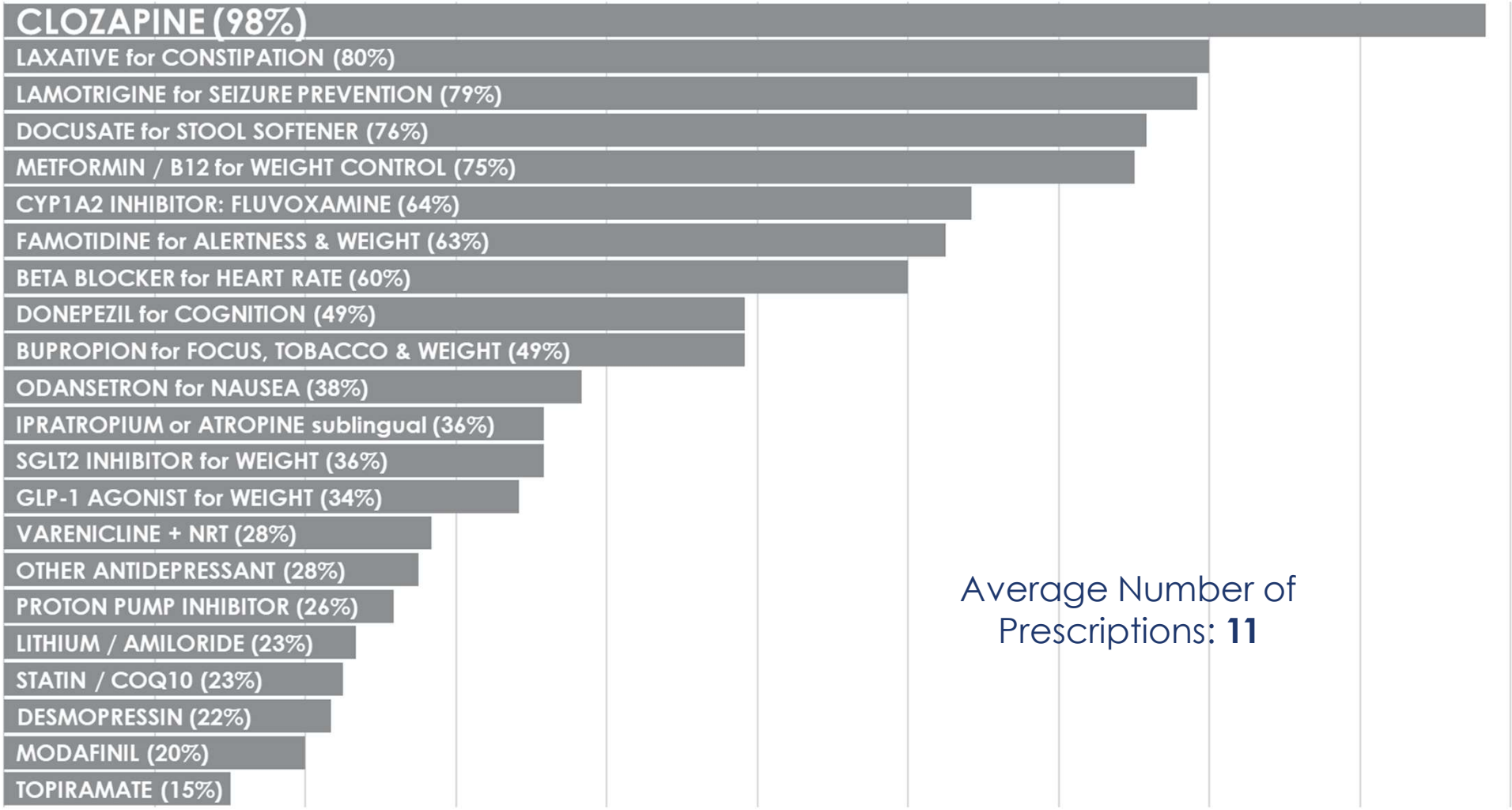
PROPORTION OF PATIENTS WITH MORE THAN 7% INCREASE IN BODY WEIGHT

Impressive Weight Change



TEAM DANIEL ON CLOZAPINE AVERAGE WEIGHT CHANGE (LB)

TEAM DANIEL OPTIMIZED REGIMEN (N=120)



Average Number of Prescriptions: **11**

Optimizing the Regimen

LORAZEPAM OR ALPRAZOLAM	14%
KLONOPIN	14%
LINZESS OR TRULANCE	13%
SYNTHROID	11%
WAKIX (PITOLISANT) Investigational	10%
MEMANTINE	8%
OTHER ANTIPSYCHOTIC	7%
GABAPENTIN	6%
BENZTROPINE	5%
NALTREXONE	5%
DEPAKOTE	4%
HYDROXYZINE	4%
GLYCOPYRROLATE	3%
FLUDROCORTISONE	3%
BUSPIRONE	2%
AMANTADINE	2%

Exercise and Engagement

- **SMI is a team sport.**
- Every Saturday morning, we have our willing patients and families come to our house for a run and seasonally swim.
- The House is magic in fostering acceptance, engagement, and trust. It has taken the therapeutic relationship to another level.
- Normalization, socialization, and befriending in a non-medical environment value cannot be overestimated.
- With COVID we keep everyone engaged via two zoom sessions:
  - A family/caregiver zoom led by physicians (Dr. Laitman and Dr. Mandel).
  - A zoom for patients led by Daniel Laitman (TEAM DANIEL'S inspiration).

Exercise Benefits Meta-Analysis

In 29 studies, 1,109 patients statistically significant improvement in:

- Total symptom severity
- Positive symptoms
- Negative symptoms
- General psychopathology
- Quality of life
- Global functioning
- Depressive symptoms

Dauwan M, étal (2016) Exercise improves clinical symptoms, quality of life, global functioning and depression in Schizophrenia : A systemic review and meta-analysis. Schizophrenia Bulletin, 42, 588-599

Team Work

In July, 2021, Team Daniel ran the Long Island Jovia Marathon: Michael Orth, *Commissioner at WC, DCMH;* Dr. Rob Laitman, Jasper Bresolin, Malachy Friel.

The Diet

- **Eat 3 meals a day – Do NOT drink your calories**
- Avoid all simple processed carbohydrates:
  - NO cookies, candy, chips, dips, cakes, ice cream, donuts
  - Minimize bread, pasta (whole grain only)and rice (small portion brown rice only)

BREAKFAST

High fiber cereal *or*
Eggs, (Veg omelet) *or*
Oatmeal with raisins

Coffee *or* tea

Milks: Almond *or* Skim
Sweeteners: Stevia, Splenda

LUNCH

Non tropical fruit
Blueberries, strawberries, blackberries, apples, plums or pears.
Greek yogurt *100-160cal*

SNACK

Unsalted nuts *or* fruit
Blueberries, strawberries, blackberries, apples, plums or pears.

DINNER

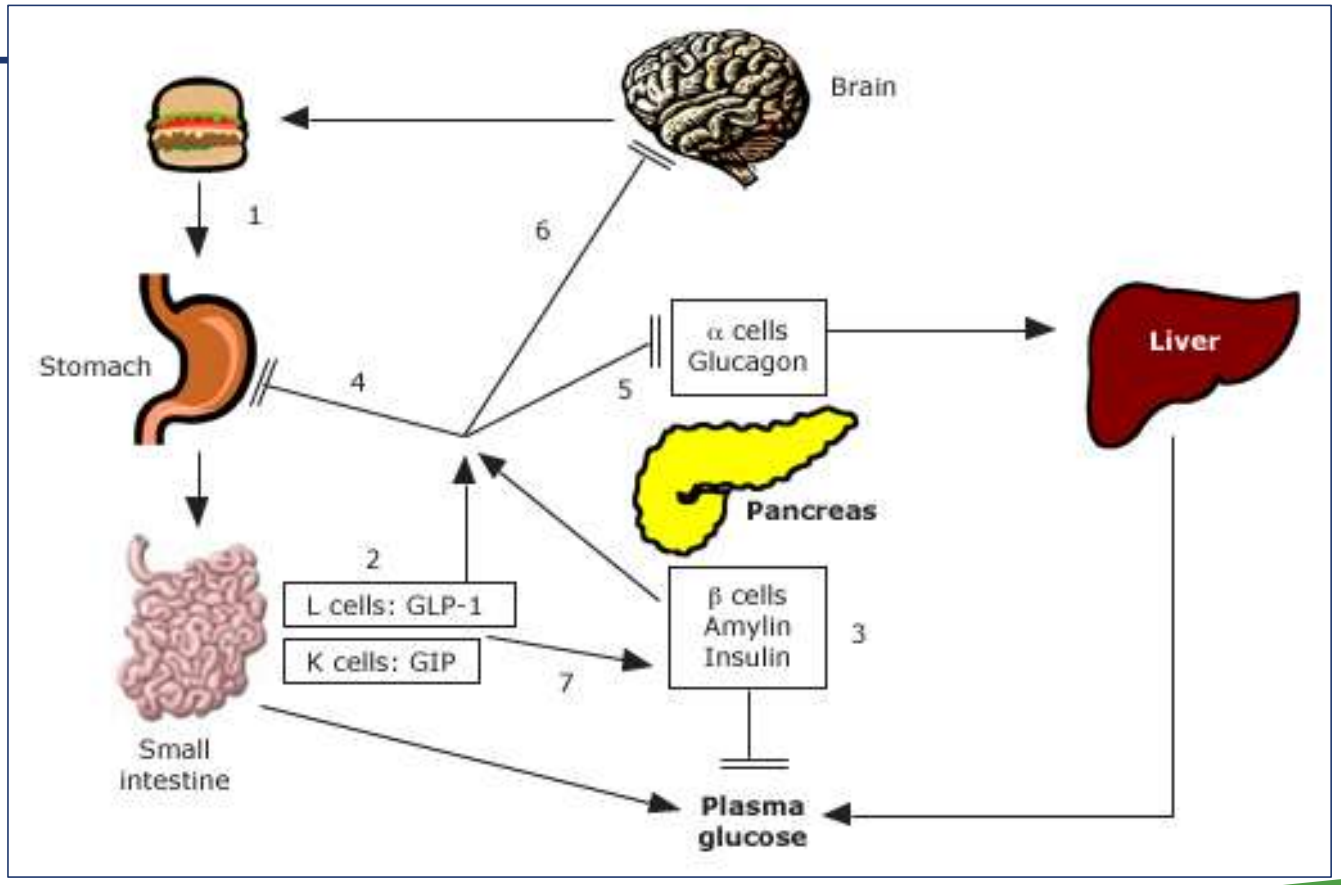
Garden salad *with only vegetables & a light low salt dressing spritzed on.*

Vegetable *like broccoli, brussel sprouts, string beans, spinach, or cauliflower.*

Protein *6-8 ounce of fish, poultry, pork, tofu, setain. or a legume : lentils, chick peas etc.*

Non tropical fruit

Multihormonal Regulation of Glucose

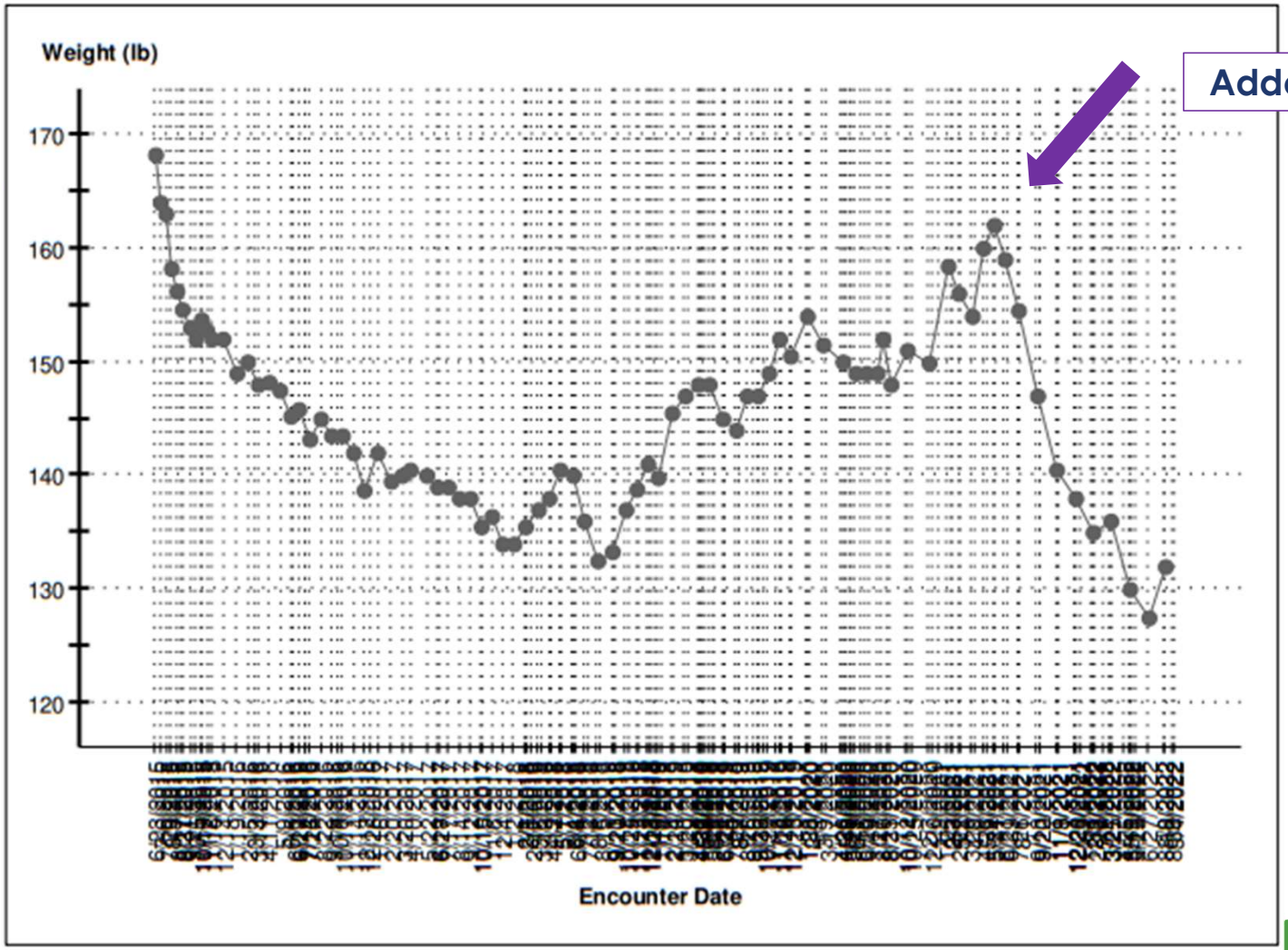


In healthy individuals…

(1) ingestion of food results in
(2) release of gastrointestinal peptides (GLP-1 and GIP) as well as
(3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on
(4) gastric emptying,
(5) glucagon release, and
(6) appetite.
(7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

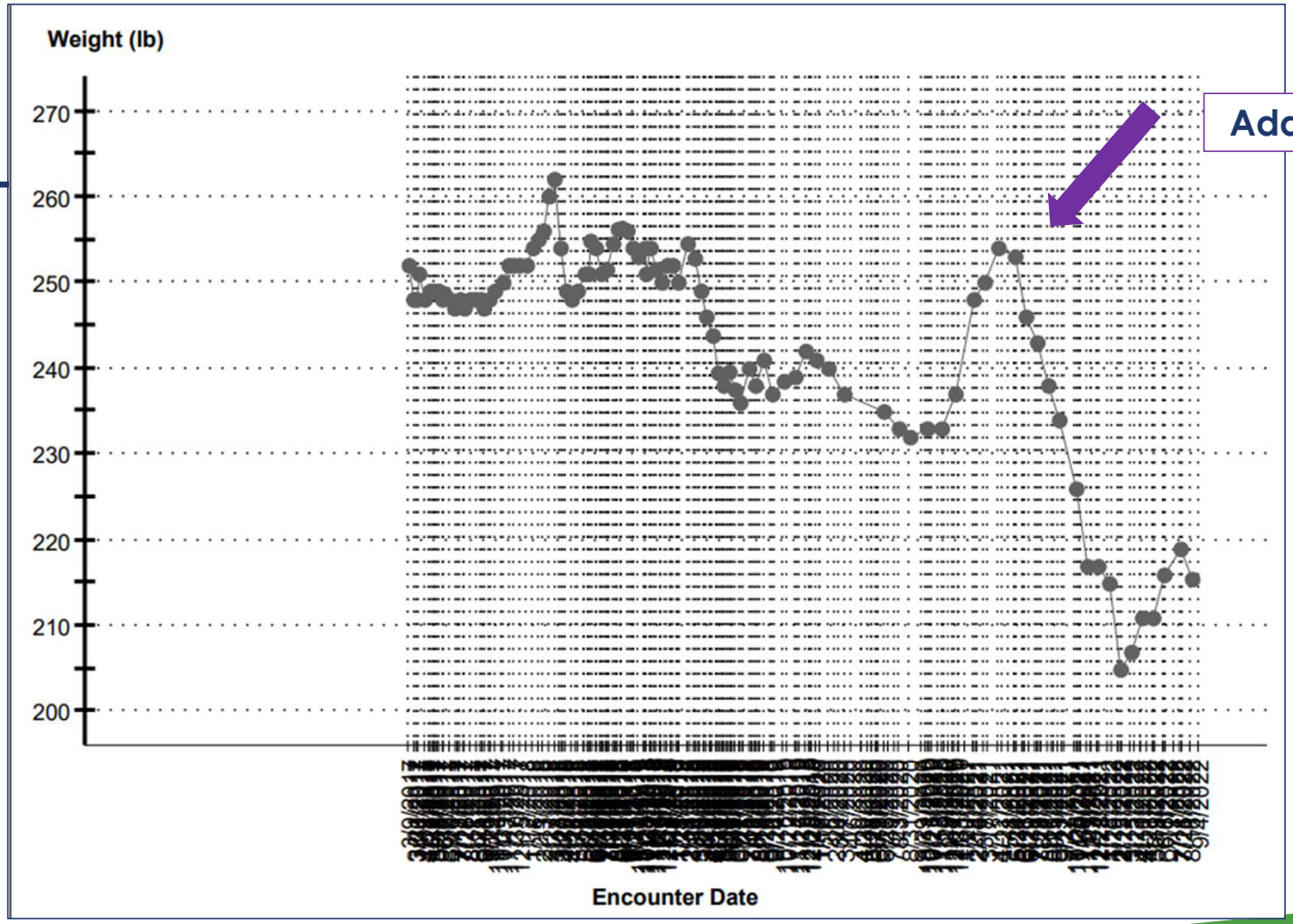
The Role of GLP-1 and GIP in Glucose Homeostasis

	GLP-1	GIP
Site of synthesis	Small intestinal L cells	Small intestinal K cells
Glucose-dependent stimulation of insulin secretion	Yes	Yes
Reduction of gastric emptying	Yes	No effect
Reduction of inappropriate glucagon secretion	During euglycemia or hypoglycemia: No effect During hyperglycemia: Suppresses glucagon	During euglycemia or hypoglycemia: Stimulates glucagon During hyperglycemia: No effect
Weight loss	Yes	Yes



Added Trulicity

Female Patient

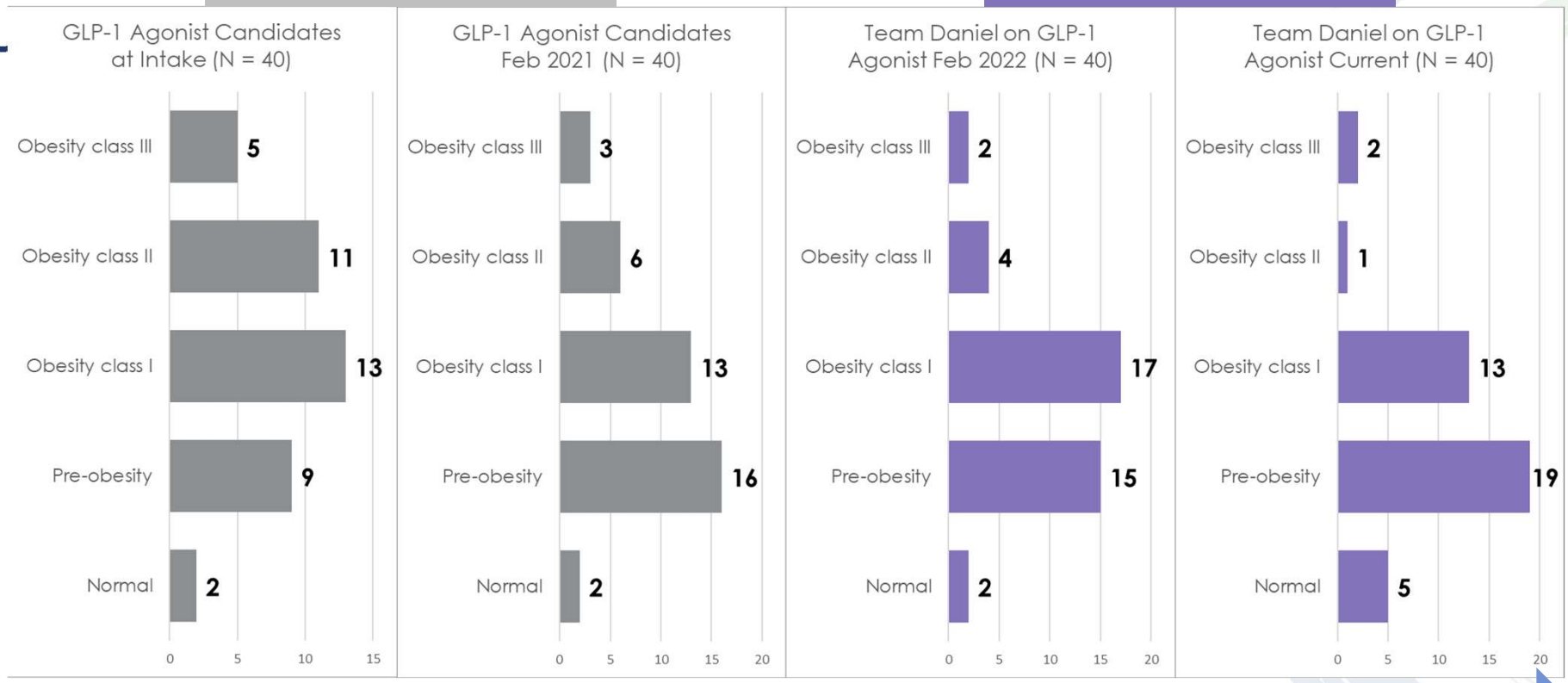


Added Trulicity

Male Patient

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% Obese	*55% Obese*	*58% Obese*	*40% Obese*

An APA and SAMHSA Initiative

AMERICAN PSYCHIATRIC ASSOCIATION

SAMHSA Substance Abuse and Mental Health Services Administration

TEAM DANIEL©

Rev. 2/2/2022

Team Daniel Clozapine Regimen Initiation Summary

		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. 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.	No changes first 2-4 weeks; keep it level. Discuss dangers of marijuana/THC. Consider 50 mg naltrexone (PM) for SUD. 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.	Smoking decreases serum levels on average 50% Discuss transition to vape or ideally NRT which is preferred. Consider Chantix or bupropion and other means of reducing dependence on nicotine. Continue to explain the value of non-smoked forms.
	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				
MONTH 2	Week 5	100 mg PM*			500 mg PM	25 mg AM			
	Week 6	125 mg PM*			500 AM/500 PM	25 mg AM			
	Week 7	150 mg PM*			500 AM/500 PM	50 mg AM			
	Week 8	175 mg PM*			500 AM/1000 PM	50 mg AM			
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.**

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AMERICAN PSYCHIATRIC ASSOCIATION

SAMHSA Substance Abuse and Mental Health Services Administration

Team Daniel Clozapine Regimen Maintenance Summary TABLE 2

Suboptimal Clozapine Results (Most Resistant Schizophrenia)	Fluvoxamine	Depression & Alertness	Cognition Improvement	Metabolic Syndrome Weight Control	Hypersalivation & Pneumonia Prevention	Lithium Carbonate ER	Neutropenia & Clozapine Toxicity
TDM OF CLOZAPINE SERUM LEVELS: 75% of patients START responding at 400 ng/mL; the threshold for Bipolar is lower. Up to 1000 ng/mL should be pursued for efficacy. With adjunct fluvoxamine, levels up to 1500 ng/mL or higher may be considered. Median Team Daniel patient serum levels are 640 ug/mL at 1 year of treatment. Statistics represent clozapine levels only, not the sum of clozapine & norclozapine. **POSITIVE SYMPTOMS**: Split clozapine dosage 2-3x daily, largest dose before bed e.g., 50mg 9am / 75mg 2pm / 125 mg 7pm. If no positive symptoms, give entire dose at bedtime. **PREVIOUS ANTIPSYCHOTICS**: slowly taper & discontinued as clozapine is titrated to therapeutic levels. **ECT**: Most effective for depression. Consider for audio & visual hallucinations. **TMS**: for negative symptoms. **ANTIPSYCHOTIC AUGMENTATION**: 1st choice-Aripiprazole for low weight gain & low sedation profile. 2nd choice-Risperdal. There is no compelling evidence that antipsychotic augmentation provides greater efficacy. Concomitant antipsychotic use can impede clozapine's efficacy & increase adverse side effects. **MINOCYCLINE ANTIBIOTIC**: 100 mg 2x daily. **AVOID**: smoking (decreases clozapine serum levels), marijuana & CBD (increases psychosis risk), herbal supplements (Unknown medication interactions).	**SSRI / OCD**: (CYP1A2 inhibitor) increases clozapine serum levels without increasing norclozapine metabolite. Goal: achieve therapeutic clozapine serum levels for adequate symptom control with lower dosage & fewer side effects. Can dramatically improve sialorrhea. **CAUTION - Medication Interaction: Seizure risk increases as clozapine serum levels increase. Fluvoxamine can double or triple clozapine levels. Anti-seizure meds (preferably lamotrigine) must be given before initiating fluvoxamine.** Starting dose: 6.25 mg pm (1/4 of 25 mg). Titrate 6.25 mg every 2 weeks. Check clozapine serum levels with each fluvoxamine increase. Slowly taper clozapine while titrating fluvoxamine. clozapine: norclozapine ratios improve. Target: clozapine: norclozpine ratio: 2:1 (or better), e.g., 640:320	**DEPRESSION** -Antidepressant: Bupropion XL 150-450 mg daily. Aids in weight loss. reduces nicotine cravings. Initiate after psychosis is reduced due to increased risk of mania. Patients must be on sufficient seizure prophylaxis (Preferably lamotrigine) due to increased seizure risk. -ECT: treatment-resistant depression **ALERTNESS** -(narcolepsy treatment): Modafinil 100-200 mg am. Cut 100 mg into 1/4 & titrate slowly, may trigger psychosis & anxiety. ADD/ADHD: often psychosis illness prodrome & misdiagnosed. Stimulants can worsen psychosis. Optimized clozapine is the best treatment for focus & attention.	H2 BLOCKER: Famotidine 100 mg 2x daily. ACETYL-CHOLINESTERASE INHIBITOR: Donepezil 5-10 mg daily (may reduce clozapine-induced constipation). NMDA Antagonist: Memantine 5-10 mg 2x daily. GUANFACINE: 1-2 mg (indicated for hypertension & inattention) Caution: can cause drowsiness & hypotension. BrainHQ, Speech therapy, DBT, CBTP, & academic courses of interest. CETCLEVELAND: Formal Cognitive Enhancement Therapy (CET) AVOID, when possible (due to adverse cognitive effects): Haldol, diphenhydramine (Benadryl), benztropine (Cogentin), hydroxyzine, benzodiazepines, and divalproex sodium (Depakote). DAILY VITAMINS: B12, Folic Acid, D3, Omega 3, CoQ10, NAC, Phosphatidyl-Choline during pregnancy for prevention.	DON'T wait for diabetic criteria. Clozapine causes impairment in glucose tolerance. METFORMIN ER 1000 BID: (Use Extended Release), start at 500 mg pm, and titrate to 1000 mg am/pm for ANY increase in weight, appetite, lipids, and liver enzymes. Exceptions: underweight, & normal: weight, lipids, glucose, and liver enzymes. For GI side effects: lower dosage &/or limit to pm (<2000 mg daily may not produce weight loss). SGLT2 INHIBITORS: Jardiance (or similar) 10-25 mg daily. GLP-1 RECEPTOR AGONISTS: weekly dulaglutide (Trulicity or similar) or semaglutide (Ozempic or similar) subcutaneous injection. DUAL GIP/GLP-1 RECEPTOR AGONIST: tirzepatide (Mounjaro or similar) subcutaneous injection weekly. Naltrexone/bupropion (Contrave) 8/90 mg pm. Topiramate 25 mg - higher doses may worsen sedation. Surgical weight loss for extreme cases. Caution: weight loss surgery can impact clozapine absorption & serum levels. Therapeutic clozapine serum level is the most significant factor in patients' ability to understand the need for a consistent exercise program. Avoid sweets, carbs, and junk foods, and never drink your calories.	**HYPER-SALIVATION**: Prevent aspiration pneumonia - a dangerous complication of clozapine therapy, far surpassing risks of severe neutropenia. Elevate the head of the bed. No food 2 hours before bed. ANTI-CHOLINERGICS: 1% sublingual atropine drops or ipratropium bromide spray 1-3 drops/puffs under the tongue at bedtime, up to 3x daily. Glycopyrrolate 1-4 mg BID. Caution: high risk of constipation & tachycardia. Mitigate with Linzess & Propranolol beta-blocker. Guanfacine 1-2 mg at bedtime. Caution: hypotension risk NAC (N-acetylcysteine) 500-1200mg BID Resistant sialorrhea: Botox submandibular & parotid salivary gland injections every 3 months.	**MOOD STABILIZER**: Administer concurrently with clozapine for persistent mood disorders. Titrate 150-300 mg weekly to a therapeutic range of 0.8-1.2 mEq/L. **NEUTROPENIA**: ANC <1500/mcL. Titrate lithium carbonate ER 150-300 mg weekly to 0.8-1.2 mEq/L until resolved. For chronic neutropenia or levels <500/mcL: filgrastim 5-10 mcg/kg/weekly. To prevent kidney damage & improve renal clearance: Use extended-release and administer once daily before bed. For doses >450mg, add amiloride 5mg am to prevent diabetes insipidus. Therapeutic Drug Monitoring (TDM) monthly/quarterly & Thyroid panel. Hypothyroidism: Use levothyroxine.	**NEUTROPENIA**: affects <3% of clozapine patients. Drops or downward trends are not concerning unless the ANC count is <1500/uL or <1000/uL for Benign Neutropenia (BEN) patients. ANC results: <1500/uL repeat test immediately following exercise & in the afternoon when the neutrophil count is highest. <1500/uL persists; add lithium carbonate ER. Repeat ANC 3x weekly. <500/uL add filgrastim. BEN ANC: <1000/uL Repeat ANC 3x weekly. If clozapine must be discontinued, in 6 months, rechallenge with prophylactic lithium. Titrate 6.25 mg of clozapine weekly. **CLOZAPINE TOXICITY**: Toxic ranges are not well established. Serum levels >1500 ng/mL may cause Seizure, hypotension, cardiovascular abnormalities, confusion, choking, shallow breathing, and severe sedation - cut dose to ½ & check levels. As clinical symptoms improve, resume dosage. **MYOCARDITIS / TACHYCARDIA**: use ultra-slow titration, and avoid Depakote. Treat resting heart rate >100 with a beta blocker.

Dr. Robert Laitman 914-629-5130 Dr. Ann Mandel Laitman 914-841-2095

Connect with TEAM DANIEL

Website: Teamdanielrunningforrecovery.org

Email: Robert S. Laitman: rslaitman@aol.com

Cell: 914-629-5130 Personal Cell Phone

Facebook: Team Daniel and the Clozapine Community

Where there is help there is hope!

TEAM DANIEL
Running for Recovery from Mental Illness

FEEDBACK

Please help us improve the Clozapine & LAI Virtual Forum by completing this survey:
http://smiadviser.org/forumfeedback

Pre-submit Cases

www.smiadviser.org/vfcases

UPCOMING VIRTUAL FORUM

LAI Topic TBA

October 5 @ 4-4:45pm ET

For additional questions and resources – join the Clozapine and LAI Centers of Excellence Exchange Community

- www.smiadviser.org/cloz_lai_signup