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Invited commentary

The EASE model for optimum use of clozapine: A clinician perspective

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Clozapine is universally recognized as the most effective antipsychotic available in essentially any setting, yet it is grossly underused (Kelly et al., 2018). Psychiatric practitioners have been trained to fear it, a reaction we term "clozaphobia". this irrational fear of clozapine is based on dogma and misinformation, and effectively discourages the use of clozapine except as a last resort for treatment-resistant psychosis. In this paper, we argue that these concerns can be addressed effectively by a) *early introduction* of clozapine in the course of the illness b) *assertive monitoring and interventions for side effects*, c) *slow titration and optimum dosing* informed by therapeutic drug concentrations; and d) *engagement and support* of patients and their caregivers. We herein discuss these principles (which may be summarized by the mnemonic EASE) for consideration by clinicians prescribing clozapine. We draw upon our experiences in our clozapine clinic ("Team Daniel") to outline these principles. Team Daniel is a recovery oriented clinical service and advocacy for individuals with severe mental illness, as part of the Bronx Westchester medical group (https://www. teamdanielrunningforrecovery.org). We would like to emphasize that our recommendations outlined here is based on our years of experience and is not necessarily to be found in published evidence-based literature. Briefly, with an N of 120 with over 1 year of follow up we experienced 73 % in meaningful recovery, a decrease in hospitalizations from 93 % in the year prior to joining the practice to 15 %, Only 22 % of our population gained greater than 7 % body weight, 82 % recovery from substance use and cannabis use, and there was a 67 % tobacco cessation rate. More details of our data from this clinic will be reported in a separate paper. For an updated review of this literature the reader is referred to other works (De Berardis et al., 2018; De Leon et al., 2021; Keshavan et al., 2022a; Meyer and Stahl, 2020; Opler et al., 2017).

1. Early introduction of clozapine

Recent literature supports the use of clozapine early in treatment. A recent meta-analysis demonstrated that the greater efficacy of clozapine relative to other antipsychotics was not dependent on the degree of treatment-resistance,

arguing for its use more generally in schizophrenia (Mizuno et al., 2020). There is evidence that patients who initiate clozapine after a longer illness duration are less likely to respond. Arguing for clozapine's use earlier and more widely are clozapine's known benefits in suicide prevention, violence, and substance abuse in schizophrenia (Meltzer, 2012) and in bipolar disorder with psychosis (Costa et al., 2020). This is especially important as this patient population experiences a first-year mortality of 24–89 times that of the general population, and much of that excess mortality is secondary to these factors (Schoenbaum et al., 2017).

2. Assertive monitoring and proactive treatment of predictable side-effects

The clinician should have a low tolerance for side effects. It is predominantly the side effect profile of clozapine that dissuades the faint of heart from prescribing it, and yet the side effects can be ameliorated with rational polypharmacy. Adjunctive medications, if wisely prescribed, can also enhance the benefits of clozapine. The acronym ABCDs of clozapine can be useful (Table 1). We list the major side effects and their treatment or circumvention in Supplementary Table 1, Supplementary Table 2, Supplementary Table 3. Supplementary Table 2 describes a typical timetable for introduction of clozapine and recommended adjunctive medications.

3. Slow titration and therapeutic drug monitoring (TDM)

Slow titration of clozapine is extremely important to provide the highest probability of toleration and thus compliance. Some of the most problematic potential side effects, such as agranulocytosis, cardiomyopathy, and myocarditis, are functions not only of dosage levels but of the rate of introduction. A gradual titration (Supplementary Table 2) allows the body to acclimate and reduces the impact of side effects such as constipation and metabolic syndrome and provides time for the clinician to ameliorate them with appropriate adjunctive medications. Because every individual metabolizes clozapine differently, it takes considerable experimentation to determine the appropriate dosage for a given patient. Titrating slowly and evaluating the result each week allows the clinician to determine the minimum effective dosage. In the Team Daniel population, the lowest quartile of schizophrenia spectrum patients is on dosages between 25 and 200 mg per day, and for our patients with bipolar disorder the range is as low as 12.5 to 62.5 mg. Slow titration also provides time for the extended cross-taper that is usually necessary when a patient who is already on another antipsychotic begins clozapine treatment, and time for the gradual introduction of anti-seizure prophylaxis. Except in a hospital setting where the requirement to gain rapid control of positive symptoms outweighs other considerations, there is no reason to accelerate clozapine titration.

Therapeutic drug monitoring is important to measure efficacy, assess compliance, and avoid toxicity. As the typical metabolic half-life of clozapine is approximately 12 h, serum concentration should be measured as 12-hour trough levels. The rate of clozapine metabolism and the dosage required to achieve therapeutic levels varies widely from person to person. Individuals of indigenous and Asian descent tend to be slow metabolizers and may require only one half the dosage required by individuals of European origin to achieve similar serum levels (Suhas et al., 2020). Inflammation, smoking, and medications that inhibit clozapine metabolism can significantly affect serum levels and thus dosing decisions.

Table 1. Side effects of clozapine. DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms.

- Agranulocytosis, Anticholinergic side effects
- Body weight increase, Blood pressure drops (orthostasis)
- Cardiovascular side effects (tachycardia, orthostasis, myocarditis) constipation,
- Drooling, Diabetes risk, Dyslipidemia, DRESS syndrome, Drowsiness
- Epileptic seizures
- Fever

The most carefully designed regimen is of no use if the patient doesn't adhere to it. The benefits of clozapine end when clozapine is stopped, and abrupt cessation risks rebound psychosis and cholinergic rebound. TDM is critical to avoid these risks, particularly for patients with anosognosia who are unlikely to comply with treatment unless closely supervised and monitored.

In addition to clozapine serum levels and the mandatory blood cell counts, the clinician needs to typically obtain lipid and metabolic panels along with HgbA1C to evaluate metabolic effects and may follow serum levels of specific medications for individual patients. Early in treatment, we follow high sensitivity C-reactive protein (HS-CRP) weekly, as this is a sensitive measure of inflammation. If this becomes elevated, troponin monitoring is helpful to assess potential myocarditis.

A modality in which TDM is particularly critical is the augmentation of clozapine with fluvoxamine (Lu et al., 2018). Clozapine's primary metabolite is norclozapine, which is largely responsible for some of the unpleasant side effects of clozapine such as sedation and sialorrhea. Metabolism of clozapine is mediated by the CYP1A2 enzyme, and we use the CYP1A2 inhibitor fluvoxamine to slow clozapine metabolism and simultaneously adjust the clozapine/norclozapine serum ratio. This must be undertaken with great care, as a fluvoxamine dose as low as 25 mg can triple clozapine levels. We typically titrate fluvoxamine at a rate of 6.25 mg – one quarter of the smallest available pill – every two weeks, with TDM at each increase. Patients must be maintained on seizure prophylaxis during and following the titration, because of the likelihood of rapid increase in, and higher sustained values of, clozapine serum level. Whereas a typical unaugmented clozapine/norclozapine ratio is about 1.3, the ratio when augmented with fluvoxamine is approximately twice that at about 2.6. When we initially began augmenting clozapine with fluvoxamine, we regarded it as a "moon shot", a means of achieving a high clozapine level for patients that required it, without incurring intolerable side effects.

4. Engagement and support

The optimal clozapine approach requires a fully engaged patient, family, and treatment team. Engagement begins before the first prescription is written. All families and patients have our private cell number and e mail and we are available 7 days a week 52 weeks a year. On site we have a psychiatric social worker expert in the care of psychotic individuals. We provide weekly psychoeducation and support via zoom and bimonthly in-person open house sessions for befriending, socializing, exercising, and normalizing in an accepting community setting.

Approximately 75 % of individuals with psychotic spectrum disorders have mild or more severe lack of insight, also called anosognosia (Keshavan et al., 2004). This cohort is disinclined to accept treatment, so it is first necessary to establish a strong and supportive relationship. Discussing the nature of the illness and the treatment with the patient and family in hopeful terms is critically important (Keshavan et al., 2022b). Even when anosognosia is not present, initial acclimatization to clozapine can be difficult, and an encouraging partnership is important in motivating treatment adherence. We start by befriending patient and family, using Amador's listen/empathize/agree/partner (LEAP) techniques (Amador, 2012). Sufferers are in pain and must be made to feel safe and accepted. We communicate to the patient and family our understanding that treatment of these disorders is never a linear progression, that there will always be setbacks and detours, and that we will not abandon the patient when they inevitably occur. Availability is an important factor in establishing confidence and trust. All our patients and families receive our personal contact information and are encouraged to reach out to us when questions or problems arise. We act as active cheerleaders for the patients.

When a therapeutic relationship cannot be established, the clinician may need to turn to court-mandated treatment to

effectively engage patients. In New York, this program is referred to as assisted outpatient treatment (AOT), also called Kendra's law. Although definitions and enforcement vary widely, the intent is court-mandated participation in treatment (Cripps and Swartz, 2018), with hospitalization enforced for non-adherence.

Family is an integral part of the treatment team and cannot be excluded from decision-making. Privacy constraints can be a barrier to treatment. We address this by actively engaging families from the beginning of the treatment. This is particularly important early in treatment when the patient is still in the grip of psychosis and cannot meaningfully participate in his or her own care.

We encourage socialization both as a therapeutic measure and as a means for information sharing and mutual support. Our patient population and their families form a community we have named "Team Daniel", after our son and first patient. Team Daniel members interact in person and online, establishing friendships, sharing resources, and dissolving the isolating barriers often experienced by sufferers of these illnesses.

5. Conclusion

While clozapine is the most effective antipsychotic, and reduces psychosis, violent behavior, suicide, and substance abuse to a greater degree than any other antipsychotic, it has been relegated to a medicine of last resort because of fear and misunderstanding. Using clozapine early in treatment, assertive monitoring, slow titration and optimum use of TDM and engaging the patient, family and treatment team can all help treatment success and change the trajectory of the illness. Optimism, optimal use of clozapine, and an integrated approach restore hope. We also hope that the experiential recommendations outlined in the EASE model will motivate empirical studies to enhance evidence-based data for use of this highly valuable treatment.

The following are the supplementary data related to this article.

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Supplementary Table 1. Side effects of clozapine in order of decreasing frequency, suggested treatments and clinical considerations. These suggested options are based on clinical experience and are not all necessarily based on systematic studies. GLP1: Glucagon like peptide-1 agonist; REMS: Risk evaluation and mitigation strategy; GCSF: Granulocyte colony, stimulating factor; ANC: absolute neutrophil count.

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Supplementary Table 2. Recommended titration schedule for clozapine and suggested approach to using supplementary medications to minimize and manage side effects. TDM: therapeutic drug monitoring. ANC: absolute neutrophil count. HSCRP: High sensitivity C-reactive protein.

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Supplementary Table 3. Therapeutic considerations during clozapine maintenance treatment. Brain HQ Intervention is an online platform that "exercises" their memory, processing speed, and attention via an interactive game format.

Declaration of competing interest

The authors have no conflicts to declare.

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View Abstract

	Side Effect	Treatment	Clinical considerations
Common	Sedation / Sleepiness	•When psychosis is well controlled: Modafinil, bupropion, high-dose famotidine	Sleep heals; up to 12 hours per day can be healthy on clozapine.
	Constipation	• Stool softeners & laxatives Polyethylene Glycol • linaclotide or plecanatide	Treat proactively to prevent bowel obstruction; do not use fiber supplements.
	Hypersalivation (drooling, especially at night)	•Atropine drops or ipratropium spray (sublingual) •Glycopyrrolate, consider salivary gland Onabotulinum toxin A	Treat proactively to prevent aspiration pneumonia. No bedtime food or drinks. Elevate the head of the bed.
	Weight gain / excessive hunger / diabetes risk	•Metformin (consider adding SGLT2 inhibitor, GLP-1 agonist)	Treat proactively within first weeks of starting clozapine.
	Elevated heart rate (high pulse)	•Beta blocker(i.e. propranolol / metoprolol / atenolol)	Treat proactively to prevent cardiomyopathy.
	Nausea / vomiting	• Ondansetron • metoclopramide secondary	Also shown to improve mood symptoms.
	Heartburn / acid reflux / nighttime "cough"	•Famotidine, proton pump inhibitor secondary	Do not use calcium carbonate which blocks clozapine absorption.
	Bedwetting / urinary urgency or frequency	•Desmopressin • mirabegron secondary	Often resolves over time, minimize bedtime liquids.
	Mild fever, sweating, increased white blood cells	•Wait and watch (treatment usually unnecessary)	Mild symptoms common during clozapine initiation, resolve over time.
	Body pain or numbness	• Slower dose escalation •Acetaminophen or ibuprofen	Occurs with large dose increases over 25mg. Hospitals and inexperienced providers often increase daily dose by 50mg at a time or more.
	Orthostasis (drop in blood pressure, dizziness, fainting, blurry vision)	•Slower dose escalation •Increase salt and water intake •Fludrocortisone if orthostasis persists, midodrine secondary	Improves over time as the body adjusts; slowing clozapine dose increase is helpful.
	Atonic seizure activity (muscles becoming limp, dropping objects, falls, poor balance) Or any type of seizure	•Lamotrigine •lacosamide, levetiracetam), gabapentin or topiramate. Valproate only as a last resort due to clozapine interaction.	Risk increases at higher clozapine serum levels. Prevent occurrence with adjunctive anticonvulsant medications. Avoid spikes in serum levels (i.e. careless use of fluvoxamine, inflammatory illnesses, abruptly quitting smoking, large dose fluctuations)
	Retrograde ejaculation (reduced sperm production)	No available treatment	Does not affect erectile function, orgasm or fertility.
	Movement disorder (dystonia, tardive dyskinesia, oculogyric crisis)	•Split clozapine dose throughout day •VMAT2 inhibitors, diphenhydramine or benztropine	Can occur at high clozapine serum levels in patients with history of non-clozapine antipsychotic use.
	Myocarditis, pericarditis, cardiac arrhythmias	•slow titration increase daily clozapine dose by 25mg each week to prevent severe side effects.	Hospitals and inexperienced providers may increase daily clozapine doses by 100mg (or more) each week which can be dangerous for many patients. Interrupting clozapine also carries risks (i.e. due to REMS or bloodwork).
Rare	Neutropenia (ANC below 1500/mL) Agranulocytosis (ANC below 500/mL)	•Retest ANC in afternoon after exercising •Adjunctive lithium, GCSF secondary	Most cases of low ANC are benign, transient and unrelated to clozapine. Historically, most interruptions in treatment have been unwarranted.
	Other rare / serious complications	Most are treatable, many patients can continue clozapine.	Examples: embolism, thrombosis, liver toxicity, NMS, pancreatitis.

Supplementary Table 1. Side effects of clozapine in order of decreasing frequency, suggested treatments and clinical considerations. These suggested options are based on clinical experience and are not all necessarily based on systematic studies. GLP1: Glucagon like peptide-1 agonist; REMS: Risk evaluation and mitigation strategy; GCSF: Granulocyte colony, stimulating factor; ANC: absolute neutrophil count.

Medication / Issue	Week 1	2	3	4	5	6	7	8	9	10	Beyond week 10
Clozapine	12.5 mg PM	25 mg PM	50 mg PM (start TDM)	75 mg PM	100 mg PM*	125 mg PM*	150 mg PM*	175 mg PM*	Increase 25 mg weekly or q 2 weeks based on symptoms and TDM. .Therapeutic range for when clozapine serum level between 350-500 ng/mL. Some patients may need o higher levels. Consider splitting dose for strong positive symptoms with 2:1 ratio bedtime to morning dose.		
Initial PRNs	*Nausea*: Ondansetron 4 - 8 mg, up to 2X daily *Salivation*: 1% Atropine drops sublingual, 1 - 3 drops at bedtime, up to 3 drops 3x daily *Acid reflux*: Famotidine (H2 blocker) 20 mg 2X daily and/or omeprazole (proton pump inhibitor, PPI)** once daily *Tachycardia*: Beta blocker e.g., propranolol, 10 mg up to 3X per day. Use 10-20 mg PRN for anxiety. *Daytime psychosis / anxiety*: Consider PRN clozapine 12.5 - 25 mg *Nocturnal enuresis* / urinary urgency: Desmopressin 0.1 mg at bedtime to start *Catatonia:* clonazepam 0.5 mg 2X daily if no response to therapeutic clozapine serum levels.										
Docusate(for constipation)			100 mg PM	Customize bowel regimen per patient symptoms. Docusate up to 400 mg as needed. Also consider Senna-S, bisacodyl, polyethylene glycol, and linaclonide if needed; avoid fiber supplements. Use Bristol Stool chart and communicate often - patients may not be forthcoming.							
Metformin ER (for weight gain)	Start within first month of treatment to prevent metabolic syndrome and weight gain. Metformin depletes B12 - add 1000 mcg daily.			500 mg PM	500 mg PM	500 mg AM / 500 mg PM	500 mg AM / 500 mg PM	500 mg AM / 1000 mg PM	500 mg AM / 1000 mg PM	1000 mg AM / 1000 mg PM	Consider dapaglifocin/ dapaglifozin+ metformin and dulaglutide (or similar) in patients with continuing weight or metabolic concerns.
Lamotrigine ER (seizure prophylaxis)	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.				25 mg AM	25 mg AM	50 mg AM	50 mg AM	Continue increasing lamotrigine 50 mg every two weeks up to 200 mg. If lamotrigine is not tolerated consider Gabapentin, levetiracetam, oxcarbazepine. Or topiramate. Depakote is NOT recommended due to increased risks / side effects. **Watch carefully for Stevens-Johnson rash with lamotrigine.**		
Other antipsychotics	Acute psychosis: Consider temporary use of olanzapine, aripiprazole, 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.					
Substance use	No changes first 2-4 weeks; keep it level. Discuss dangers of marijuana / THC. Consider 50 mg naltrexone (PM) for substance use disorder (SUD).				As clozapine becomes effective, discuss life goals and how to transition from harmful substances. Recommend drug counseling, dialectical behavior therapy, possibly 12-step programs. Avoid short-acting benzodiazepines like alprazolam. PRN lorazepam or clonazepam (low dose) for acute symptoms only during initial clozapine titration; discontinue after acute symptoms subside.					
Smoking				Consider nicotine replacement therapy.				Consider varenicline or bupropion and other means of reducing dependence on nicotine. Continue to explain the value of non-smoked forms.			

Notes:

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

Cautions:

- Smoking decreases clozapine serum levels on average 50%.
- Special handling will be required for 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 benign ethnic neutropenia 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 used for patients 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.

Supplementary table 2. Recommended titration schedule for clozapine and suggested approach to using supplementary medications to minimize and manage side effects. TDM: therapeutic drug monitoring. ANC: absolute neutrophil count. HSCRP: High sensitivity C-reactive protein

Suboptimal Clozapine Response		Depression & Alertness	Cognitive deficits/ADHD	Metabolic Syndrome Weight Control	Hypersalivation & Pneumonia Prevention	Lithium Carbonate ER	Neutropenia Clozapine Toxicity Myocarditis
THERAPEUTIC DRUG MONITORING OF CLOZAPINE SERUM LEVELS: 75% of patients START responding at 400 ng/mL; the threshold for Bipolar is lower. Up to 1000 ng/mL can 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 auditory & visual hallucinations. **TMS**: for negative symptoms. **ANTIPSYCHOTIC AUGMENTATION**: 1st choice-Aripiprazole for low weight gain & low sedation profile. 2nd choice-Risperidone. **There is no compelling evidence that antipsychotic augmentation provides greater efficacy.** Concomitant antipsychotic use can impede clozapine's efficacy & increase adverse side effects. **MINOCYCLINE/DOXYCYCLINE ANTIBIOTIC**: 100 mg 2x daily. **AVOID**: smoking (decreases clozapine serum levels), marijuana & cannabidiol (increases psychosis risk), herbal supplements (Unknown medication interactions).	**FLUOXAMINE** (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. **Target:** -clozapine: norclozapine ratios improve. -clozapine: norclozpine ratio: 2:1 (or better), e.g., 640:320	**DEPRESSION: ANTI-DEPRESSANT** 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 part of psychosis illness prodrome and can be misdiagnosed.** Stimulants can worsen psychosis. Optimized clozapine is the best treatment for focus & attention.	**H3 receptor antagonist**: 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 & ADHD/ inattention) **CAUTION:** can cause drowsiness & hypotension. **THERAPY:** BrainHQ[1], Speech therapy, dialectical behavior therapy, cognitive behavior therapy for psychosis, & academic courses of interest. Cognitive Enhancement Therapy **AVOID:** when possible (due to adverse cognitive effects): Haloperidol, diphenhydramine, benztropine, hydroxyzine, benzodiazepines, and divalproex sodium.	**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**: Empagliflozin 10-25 mg daily. **GLP-1 RECEPTOR AGONISTS**: weekly dulaglutide or semaglutide subcutaneous injection. **DUAL GIP/GLP-1 RECEPTOR AGONIST**: tirzepatide subcutaneous injection weekly. -Naltrexone/bupropion 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. **DAILY VITAMINS:** B12, Folic Acid, D3, Omega 3, CoQ10, N-acetylcysteine, Phosphatidyl-Choline during pregnancy for prevention of psychosis **AVOID**: sweets, carbs, 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 constipation with Linaclotide & tachycardia with beta-blocker Propranolol (or similar) -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. 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 of Lithium: monthly/quarterly & Thyroid panel. **HYPO-THYROIDISM:** 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 granulocyte colony-stimulating factor (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.