TEAM DANIEL©

Rev. 2/2/2022

Team Daniel Clozapine Regimen Initiation Summary

<table>
<tr><th></th><th></th><th>Clozapine</th><th>Initial PRN's</th><th>Colace
(Constipation)</th><th>Metformin ER
(Weight Control)</th><th>Lamotrigine ER
(Seizure Prophylaxis)</th><th>Other Anti-psychotics</th><th>Substance Use</th><th>Smoking</th></tr>
<tr><td rowspan="4">MONTH 1</td><td>Week 1</td><td>12.5 mg PM</td><td rowspan="16">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</td><td></td><td rowspan="3">Start within first month of treatment to prevent metabolic syndrome and weight gain.</td><td rowspan="4">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.</td><td rowspan="5">Acute psychosis: temporarily consider Zyprexa, Abilify or risperidone; to be discontinued after a therapeutic clozapine level is reached.</td><td rowspan="4">No changes first 2-4 weeks; keep it level.
Discuss dangers of marijuana/THC.
Consider 50 mg naltrexone (PM) for SUD.</td><td rowspan="3">Smoking decreases serum levels on average 50%</td></tr>
<tr><td>Week 2</td><td>25 mg PM</td><td></td></tr>
<tr><td>Week 3</td><td>50 mg PM (Start TDM)</td><td>100 mg PM</td></tr>
<tr><td>Week 4</td><td>75 mg PM</td><td rowspan="13">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.</td><td>500 mg PM</td><td rowspan="4">Discuss transition to vape or ideally NRT which is preferred.</td></tr>
<tr><td rowspan="4">MONTH 2</td><td>Week 5</td><td>100 mg PM*</td><td>500 mg PM</td><td>25 mg AM</td><td rowspan="12">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.</td></tr>
<tr><td>Week 6</td><td>125 mg PM*</td><td>500 AM/500 PM</td><td>25 mg AM</td><td rowspan="11">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.</td></tr>
<tr><td>Week 7</td><td>150 mg PM*</td><td>500 AM/500 PM</td><td>50 mg AM</td></tr>
<tr><td>Week 8</td><td>175 mg PM*</td><td>500 AM/1000 PM</td><td>50 mg AM</td><td rowspan="9">Consider Chantix or bupropion and other means of reducing dependence on nicotine. Continue to explain the value of non-smoked forms.</td></tr>
<tr><td rowspan="4">MONTH 3</td><td>Week 9</td><td rowspan="8">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.</td><td>500 AM/1000 PM</td><td rowspan="8">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.</td></tr>
<tr><td>Week 10</td><td>1000 AM/1000 PM</td></tr>
<tr><td>Week 11</td><td rowspan="6">Consider Farxiga/Xigduo and Trulicity (or similar) in patients with continuing weight or metabolic concerns.

Metformin depletes B12 - add 1000 mcg daily.</td></tr>
<tr><td>Week 12</td></tr>
<tr><td rowspan="4">MONTH 4</td><td>Week 13</td></tr>
<tr><td>Week 14</td></tr>
<tr><td>Week 15</td></tr>
<tr><td>Week 16</td></tr>
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*** 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.**

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 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 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/DOXYCYCLINE 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. **Target:** -clozapine: norclozapine ratios improve. -clozapine: norclozpine ratio: 2:1 (or better), e.g., 640:320	**DEPRESSION: ANTI-DEPRESSANT / SSRI:** 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 & ADHD/ inattention) **CAUTION:** can cause drowsiness & hypotension. **THERAPY:** 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 SMI prevention in fetus.	**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, 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 Linzess & 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 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.

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