How to Provide Psychiatric Consultation for Patients on Clozapine

Conflict of Interest: The author had no conflict of interest to disclose

Learning Objectives:

1) Appreciate the role of CL psychiatrists in maintaining clozapine
2) Recognize pharmacokinetic factors that affect clozapine effectiveness and risk of toxicity
3) Learn strategies to prevent and manage adverse effects of clozapine

Step 1: Appreciate the unique role of clozapine

- Clozapine is effective for treatment refractory schizophrenia, aggression in dementia, and psychosis in Parkinson and related disorders.
    - Ongoing need for clozapine may be questioned in cases of sedation, delirium, pneumonia, seizures, and other adverse effects.
    - Consulting for patients on clozapine involves educating about clozapine being more effective than other antipsychotics in specific cases and about strategies for managing treatment-limiting adverse effects.
    - If clozapine doses have been missed for more than 48 hours clozapine will need to be gradually retitrated. Educating about swift initiation of clozapine at admission to avoid retitration can prevent clinical relapse
- If a decision is made to discontinue clozapine, it should not be abruptly discontinued (unless myocarditis or severe neutropenia are present); it should be gradually tapered over 1-2 weeks. Sudden discontinuation can lead to exacerbation of underlying psychiatric illness, clozapine-withdrawal catatonia, and cholinergic rebound
    - Treatment of clozapine withdrawal catatonia includes resuming clozapine in addition to standard treatment for catatonia. Even low doses of clozapine can reverse the course of a clozapine-withdrawal catatonia.
    - reverse the course of a clozapine-withdrawal catatonia.

Step 2: Learn basic clinical pharmacology of clozapine

- 95% protein bound; half-life 4-8 hours; extensive first pass effect; 45-65% bioavailable; available as a tablet and as an oral suspension
- Clozapine is typically initiated at 25 mg PO QHS nightly and maintained at this dose for 3-4 days. It is conservatively titrated as follows: 50 mg nightly for 3-4 days → further increases of 25 mg twice weekly until a target dose of 300 mg is reached (100 mg in elderly). Levels should then be checked and dose adjusted based on clinical response and drug levels (see below)
    - Standard daily dose of clozapine: 300-600 mg/day; maximum daily dose of 900 mg/day.
        i. In elderly patients target dosing is 100-200 mg/day
        ii. In Parkinson and related disorders target dose is approximately 50 mg/day
    - Dangers of rapid titration include sedation, hypotension, seizures, agranulocytosis, neuroleptic malignant syndrome, mucus plugs and subsequent respiratory collapse

- Initial dose and speed of titration can be adjusted based on risk factors for adverse effects, tolerability and ability to monitor the patient. For example, an initiation dose of 6.25 mg or 12.5 mg nightly may be trialed in elderly patients with hypotension rather than 25 mg nightly.

- Therapeutic drug monitoring optimizes effectiveness and prevents adverse events. A trough steady-state concentration of 350–600 μg/L is recommended in schizophrenia.
- Clozapine is primarily metabolized in the liver by the cytochrome P450 (CYP P450) isoenzyme 1A2 into norclozapine
  - Systemic inflammation, infection [e.g., COVID-19 (1)], and nicotine discontinuation can decrease CYP1A2 activity potentially leading to higher levels and possible clozapine toxicity
    i. In COVID-19 and other respiratory infections with a systemic inflammatory response (evidenced by fever, increase in CRP) decrease dose of clozapine by at least 50%
    ii. Tobacco induces CYP1A2 and increases metabolism of clozapine; abstaining from smoking in the hospital → decreases in clozapine metabolism → potentially leading to higher levels/toxicity; consider decreasing dose of clozapine during hospitalization.
  - Some East Asians may be slow metabolizers of clozapine (data from Korean, Chinese, Vietnamese populations). Lower doses than listed above are effective.
  - Important drug interactions with clozapine are listed in Table 1.

Step 3: Describe adverse effects of clozapine and their management

- Clozapine has many non-serious adverse effects. The serious and fatal adverse effects of clozapine are seizures, myocarditis, and agranulocytosis
- The prevention and management of common adverse effects encountered by CL psychiatrists are described in Table 2.

References

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Table 1: Important drug interactions with clozapine (2)

Medications/Substances	Effects
Cigarette smoking Carbamazepine, rifampin, phenytoin, phenobarbital, St. John's Wort	May ↓ reduce clozapine levels via CYP 1A2 or 3A4 induction resulting in decreased efficacy of clozapine
Fluvoxamine, ciprofloxacin, oral contraceptives, caffeine antidepressants: (fluoxetine, escitalopram, paroxetine, duloxetine, sertraline), antibiotics: (erythromycin), cimetidine, quinidine, terbenafine	May ↑ increase clozapine levels via CYP 1A2 or 2D6 inhibition leading to adverse reactions
Anticholinergics (e.g., benztropine, diphenhydramine, hydroxyzine)	Additive anticholinergic activity. Monitor closely for significant anticholinergic adverse effects (e.g., constipation, hypotension).
Lithium	Combined use is associated with neurotoxicity (delirium, movement disorders, myoclonus, and seizures)
Bone marrow suppressants (e.g., antineoplastics)	Caution due to increased risk and/or severity of bone marrow suppression.
CNS depressants and general anesthesia (e.g., alcohol, opioids, benzos)	Caution because of additive CNS depressant effects including respiratory effects
Medications that lower seizure threshold (e.g., bupropion)	Extreme caution when coadministering with clozapine due to increased risk of seizures
Highly protein bound drugs (e.g., warfarin, digoxin)	Clozapine may increase levels of protein bound drugs and vice versa. Adjust dose if necessary.

Table 2: Prevention, and management of clozapine related adverse effects

	Description	Prevention/Monitoring	Management
Sialorrhea	Increases risk of aspiration pneumonia Stigmatizing Thought to be due to muscarinic-4 antagonism, alpha-2 antagonism with unopposed beta agonism, decreased laryngeal peristalsis, decreased swallowing via reduction of GI motility	None	Cover pillow with towel Elevate head of bed and encourage sleeping on side reduces risk of aspiration Ipratropium oral spray 0.06% up to 3 sprays TID → Ophthalmic atropine 1% up to 2 drops TID sublingually → Oral glycopyrrolate 2-4 mg PO QHS → Terazosin 1-2 mg PO QHS Botox in refractory cases

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	Description	Prevention/Monitoring	Management
Constipation, ileus, bowel perforation	50-80% prevalence of constipation Due to anticholinergic and antiadrenergic effects Risk factors: high dose, high level, concomitant administration with other anticholinergic medications Presentation: constipation, abdominal distension, nausea, emesis Diagnosis: subjective report, exam, abdominal X-ray, CT of abdomen	Patients with schizophrenia may not report symptoms due to higher pain thresholds and negative symptoms. Regular inquiry into bowel function is necessary. Hydration High fiber diet Exercise Start stool softeners or laxatives in patients at high risk Docusate → polyethylene glycol → sennakot or dulcolax → lubiprostone	Constipation and ileus: Docusate → polyethylene glycol → bisacodyl → sennakot or dulcolax → magnesium citrate/other enemas/manual disempaction Obstruction: nasogastric suction; surgery may sometimes be necessary
Clozapine toxicity	Delirium, neutropenia, orthostatic hypotension, tachycardia, ileus, urinary retention, mydriasis/miosis, hypersalivation, and seizures.	Recognize of drug-drug and drug disease interactions that can lead to elevated clozapine levels and clozapine toxicity; prophylactically decrease clozapine doses	Decrease or hold dose of clozapine. Check level. May take several days for results to be available but level aids in confirming suspected clozapine toxicity)
Seizures	Prevalence of 3.5-8 % Tonic-clonic seizures are most common Risk factors: Epilepsy High doses (doses > 600 mg/day) (3) Rapid titration during initiation phase	Prophylaxis with anticonvulsants for patients with: Seizure disorder myoclonic jerks (may be precursor to generalized tonic clonic seizures for patients on clozapine) Paroxysmal spike/sharp wave discharges Clozapine plasma level > 500 ug/L Clozapine dose > 500 mg/day	Obtain EEG Neurology consultation Add anticonvulsant (e.g., valproic acid) Clozapine rarely needs to be discontinued

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<table>
<tr><th></th><th>Description</th><th colspan="2">Prevention/Monitoring</th><th>Management</th></tr>
<tr><td>Neutropenia</td><td>Rare, idiosyncratic reaction
Makes body vulnerable to bacterial infections. Frequently present with fever, headache, cough, sore throat, bleeding gums or sepsis
The Clozapine REMS program provides centralized clozapine access to minimize the risk of clozapine-associated severe neutropenia
Benign ethnic neutropenia (BEN) is common in people of African or Eastern Mediterranean heritage. Alternate monitoring parameters exist for those with established BEN
For patients who have been on long-term clozapine without neutropenia and have new onset neutropenia with other constitutional symptoms, premature attribution of neutropenia to clozapine should be avoided. To this end, a broad differential diagnosis and thorough work-up for neutropenia is warranted.</td><td colspan="2"><table>
<tr><th colspan="2">Severity</th><th>Monitoring</th><th>Management</th></tr>
<tr><td>Normal</td><td>ANC >1500/mcL</td><td>Weekly from initiation to 6 months
Every 2 weeks from 6 to 12 months
Monthly after 12 months</td><td>Continue treatment</td></tr>
<tr><td>Mild</td><td>ANC 1000-1499/mcL</td><td>3x/week monitoring until ANC ≥ 1500/µl</td><td>Continue treatment</td></tr>
<tr><td>Moderate</td><td>ANC 500-999/mcL</td><td>Daily until ANC ≥ 1000/µl then, 3x/week until ANC ≥ 1500/µl</td><td>Interrupt treatment for suspected clozapine induced neutropenia
Hematology consultation
Consider filgrastim or lithium</td></tr>
<tr><td>Severe</td><td>ANC < 500/mcL</td><td>Daily until ANC ≥ 1000/µl then, 3x/week</td><td>Interrupt treatment for suspected clozapine induced neutropenia
Transfer to hospital
Place in reverse isolation
Administer filgrastim
Aggressively work up signs and symptoms
Report to Clozapine REMS</td></tr>
</table>
For patients on chemotherapy
Psychosis can interfere with cancer care management and is distressing; clozapine should ideally be continued if the patient is well established on this treatment (4); in order to do so Clozapine REMs program will need to be contacted
Multidisciplinary team discussion with heme-onc regarding alternate monitoring parameters, threshold for discontinuation of clozapine, and increased frequency of blood draws
Consider initiation of filgrastim during neutropenic nadir of chemotherapy to support neutrophil count and facilitate both clozapine and chemotherapy regimens</td></tr>
</table>

	Description	Prevention/Monitoring	Management
Myocarditis	1-3% prevalence High mortality (10 – 30%) Typically seen in first 4 weeks post-initiation Most likely IgE mediated hypersensitivity reaction Presentation: chest pain, palpitations, dyspnea, tachycardia Diagnosis: History and exam along with CRP, cardiac enzymes, eosinophil count, ECG findings, CXR, cardiac echo (5)	Monitor vitals, cardiac enzymes, and CRP weekly during first 4 weeks of titration Obtain baseline ECG	Discontinue clozapine and admit to intensive care unit Supportive use of medications to improve cardiac functioning and minimize the risk of cardiac failure such as diuretics, beta-blockers, and ACE inhibitors, corticosteroids