Considerations in Continuing Clozapine in an Aging Medically Ill Patient with Treatment Refractory Schizophrenia: A Case Report

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Background

Clozapine is associated with reduced all-cause mortality for patients with treatment resistant schizophrenia (TRS) (Wimberley, 2017). Clozapine is underutilized in patients with treatment refractory schizophrenia and particularly those with medical multimorbidity (Warnez, 2014). Guidance on managing specific side effects such as agranulocytosis is available through clozapine REMS program; however, managing clozapine in an acutely ill patient is less described. We describe a case of an aging veteran on long term clozapine maintenance and considerations in continuing clozapine during an inpatient medical hospitalization for cancer treatment.

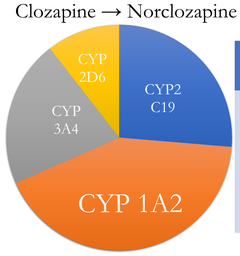
Case

A 82 year-old male veteran with history of treatment refractory schizophrenia, stable on clozapine 400mg nightly for over 30 years, with medical comorbidities including hypertension, Type 2 Diabetes Mellitus, Chronic Kidney Disease stage 3, Asthma, Coronary Artery Disease was admitted for surgical resection of Squamous Cell Carcinoma of right ear. Patient underwent a total right auriculectomy, parotidectomy, and neck dissection. His post operative course was complicated by uncontrolled hypertension, ileus, delirium and a fall resulting in rib fractures treated with rib plating, intensive care unit (ICU) admissions for respiratory failure treated with mechanical ventilation, tracheostomy and subsequently aspiration pneumonia. Patient was maintained on clozapine 400 mg nightly upon admission with a baseline clozapine level of 368 mcg/L. After the development of ileus and in anticipation of interaction with erythromycin prescribed for gastric motility, clozapine was lowered to 300 mg po qhs resulting in a level of 176 mcg/L. Of note, Patient had a history of psychotic decompensation 2 years prior in the context of clozapine dose reduction to 250 mg nightly with corresponding level of 175 mcg/L during an inpatient hospitalization for symptomatic COVID-19 pneumonia. ANC ranged from 6k-9k. Patient's clozapine dose was gradually increased with close clinical follow up monitoring daytime sedation, sialorrhea, bowel movement patterns in correlation with clozapine levels.

Clozapine Metabolism

Clozapine → Norclozapine

Metabolic Ratio (MR) = Serum Clozapine / Serum Norclozapine



MR ≤1	MR 1.32	MR ≥2
• CYP 450 Inducer • Rapid metabolizer	• Avg • Extensive metabolizer	• CYP 450 Inhibitor • Slow metabolizer • Acute

Figures

Day 5
Psych Consult, Continue Home Clozapine 400mg

Day 6
Rib Fractures from Fall S/p Surgery and SICU Transfer

Day 7
Gut Hypomotility, Erythromycin x 5 Days, Clozapine Decreased to 300mg; Lvl 368/199 MR 1.8

Day 13
Erythromycin Completed; Clozapine Increased to 350mg; Lvl 140/270 MR 0.51

Day 16
AKI on CKD Worse, Concern for Sedation, Clozapine Decreased to 300mg; Lvl 176/265 MR 0.66

Day 18
Remains in ICU, Aspiration PNA, Started Meropenem x 7 days, Delirium

Day 24
Hypercarbic Respiratory Failure, Mechanical Ventilation, Completed Meropenem

Day 31
Downgraded to GMED, Delirium, Clozapine Increased to 325 mg Lvl 185/158 MR 1.17

Day 34
Hypernatremia, Hypoxia, Severe Anemia, Back to ICU, Delirium

Day 36
Delirium, Distressing Hallucinations, Clozapine Titrated to 350mg Split Dosing

Day 39
Improved Delirium, Downgraded to Step Down, Ventilator Liberation to Trach Collar

Day 73
Transferred to GMED, New Aspiration PNA Started Ceftriaxone

Day 78
Atropine Drops for Sialorrhea; Clozapine 350 mg Lvl 386/209 MR 1.84

Day 84
Hospital Discharge, Delirium Resolved, At psychiatric Baseline, Clozapine 350 mg

Hospital Course

Clozapine-Drug Interactions and Prescription Recommendations [4]

Medication	Examples	Recommendation when Adding to Clozapine	Recommendation when Removing to Clozapine
Strong 1A2 Inhibitor	Fluvoxamine, Ciprofloxacin, Enoxacin	Use 1/3 of clozapine dose	Increase clozapine based on clinical response
Moderate/Weak 1A2 Inhibitor	Oral contraceptives, Caffeine	Monitor for SE. Consider reducing clozapine dose	Monitor for lack of effect. Consider increasing clozapine dose
Moderate/Weak 3A4 Inhibitor	Erythromycin, Diltiazem, fluconazole, Grapefruit Juice, Fosamprenavir, Amprenavir,	Monitor for SE. Consider reducing clozapine dose	Monitor for lack of effect. Consider increasing clozapine dose
Moderate/Weak 2D6 Inhibitor	Duloxetine	Monitor for SE. Consider reducing clozapine dose	Monitor for lack of effect. Consider increasing clozapine dose
Strong 3A4 Inducer	Carbamazepine, Phenytoin, Phenobarbital, Rifampin	Monitor for Decreased effect. Consider increasing clozapine dose	Monitor for SE. Consider reducing clozapine dose
Moderate 1A2 Inducer	N/A	Monitor for Decreased effect. Consider increasing clozapine dose	Monitor for SE. Consider reducing clozapine dose
Moderate/Weak 3A4 Inducer	Oxcarbazepine, St. John's Wort	Monitor for Decreased effect. Consider increasing clozapine dose	Monitor for SE. Consider reducing clozapine dose

Discussion

Acute Inpatient hospitalization in a geriatric patient with multimorbidity presents evolving challenges. This case demonstrates some of the challenges of managing clozapine. Beyond monitoring for agranulocytosis, monitoring for side effects such as gut hypomotility, drug-drug interactions ranging from QTc prolongation to effects on clozapine metabolism (Prior, 2003) anticholinergic burden contributing to delirium, sedation burden in context of post-surgical pain management, and aspiration risk are important.

Clinical Considerations

- Drug-Drug Interactions and Synergistic QT prolongation
- Effects of Tobacco Smoking
- Effects of Inflammation or Infection
- Myocarditis
- Myelosuppression or Neutropenia
- Ileus/Intestinal Hypomotility
- Sialorrhea
- Cumulative Anticholinergic Burden

Conclusion

This case demonstrates some of the unique challenges in continuing clozapine during an inpatient admission. Through greater familiarity with these factors, CL psychiatrists can ensure ongoing access to a life saving medication for treatment resistant schizophrenia (TRS).

References

1. Wimberley T, MacCabe JH, Laursen TM, et al.: Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. Am J Psychiatry 2017; 174:990–998
2. Warnez S, Alessi-Severini S. Clozapine: A review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014;14:102.
3. Prior TI and Baker GB. Interactions between the cytochrome P450 system and the second-generation antipsychotics. J Psychiatry Neurosci. 2003 Mar; 28(2): 99-112
4. Correll, C U et al. "A Guideline and Checklist for Initiating and Managing Clozapine Treatment in Patients with Treatment-Resistant Schizophrenia." CNS drugs vol. 36,7 (2022): 659-679.