Successful Continuation of Clozapine Treatment During Liver Transplantation

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Background

- There are few reports of patients with psychotic disorders undergoing solid organ transplantation (SOT).
- Evidence suggests that the majority of patients with psychotic disorders can successfully undergo successful SOT without complication, such as psychotic decompensation, medication noncompliance, or graft loss.[1]
- Further consideration is required for patients with psychotic disorders treated with clozapine in SOT due to potential drug-drug interactions between clozapine and post-transplant medications including agranulocytosis, QT prolongation, lowering of seizure threshold, and hyperglycemia.
- We report a case of a patient with schizophrenia on clozapine undergoing successful liver transplantation (LT).
- We outline the potential considerations regarding the risk of synergistic drug-drug interactions in managing a patient on clozapine post-LT.

Case Description

- 59 year old man with treatment-resistant schizophrenia stable on clozapine 100 mg and sertraline 100 mg daily for many years.
- He had cirrhosis secondary to non-alcoholic steatohepatitis, as well as hypertension, hyperlipidemia, and diabetes mellitus.
- He underwent successful LT and received methylprednisolone bolus intraoperatively, followed by tacrolimus, mycophenolate mofetil (MMF), and prednisone postoperatively.
- He was initially continued on his home dose of clozapine daily.
- On postoperative day (POD) 7, the patient had hyperverbal speech and disorganized thought process that was treated with oral lorazepam 1 mg at bedtime and 0.5 mg q6h PRN for agitation/restlessness.
- Although sleep improved, the patient then developed elevated mood, increased energy, and tangential thought process on POD 10, which was treated successfully by uptitrating his clozapine to 150 mg daily.
- 7 months later, his schizophrenia was stable and he had no reported adverse drug reactions. He did not develop agranulocytosis in his post-LT course.

Common LT Drugs	Indication	Clozapine Interactions
Corticosteroids	Induction immunosuppression	Hyperglycemia
Tacrolimus (Calcineurin inhibitor)	Maintenance immunosuppression	Agranulocytosis Seizures
Mycophenolate Mofetil (Antiproliferative agent)	Maintenance immunosuppression	Agranulocytosis
Sulfamethoxazole/ Trimethoprim	Pneumocystis pneumonia prophylaxis	QT prolongation Agranulocytosis
Valacyclovir Valganciclovir	Cytomegalovirus prophylaxis	Agranulocytosis
Fluconazole	Fungal infection prophylaxis	QT prolongation

Table 1. Immunosuppressive and infection prophylaxis agents commonly used following liver transplantation (LT) and their potential synergistic drug-drug interactions with clozapine.

Case Report	Transplant Type	Psychotropic Medications	Transplant Medications	Outcome
Lim et al. (2016), *Asian Journal of Psychiatry*	Renal	Clozapine 200mg daily	No specifics given	No synergistic side effects reported
Harrington et al. (2008), *Psychosomatics*	Renal	Clozapine 350mg bid Clonazepam 0.5mg tid Citalopram 40mg daily Benztropine 1mg qhs	Tacrolimus Mycophenolate Prednisone	No synergistic side effects reported
Wright et al. (2021), *Psychooncology*	HCST	Clozapine	Cyclophosphamide Tacrolimus Mycophenolate	WBC/ANC 0 for 25 days, recovered on home clozapine dose
Burlingham et al. (2016), *Progress in Neurology and Psychiatry*	HCST	Clozapine 200/300mg Amisulpride 200mg bid	Melphalan	WBC/ANC of 0, fully recovered despite home clozapine dose
Rosenberg et al. (2007), *American Journal of Psychiatry*	HCST	Clozapine 300mg bid Lithium 1800mg qhs	No specifics given	WBC/ANC of 0, fully recovered despite home clozapine dose

Table 2. Case reports of successful continuation of clozapine in solid organ transplant and hematopoietic stem cell transplant (HCST).

Discussion

Clozapine and liver disease risk

- Clozapine has the highest risk of metabolic side effects among antipsychotics and could contribute to development of non-alcoholic fatty liver disease (NAFLD), which could progress to hepatic steatosis, cirrhosis, and need for LT.[2]

Agranulocytosis

- Clozapine could synergistically induce agranulocytosis in combination with post-LT myelosuppressive agents (Table 1).
- Our case demonstrates that clozapine can be safely continued without the synergistic induction of agranulocytosis, adding to case reports of clozapine being successfully continued in SOT and hematopoietic stem cell transplant (HCST) (Table 2).
- We monitored CBC and ANC daily for 1 week post-transplantation, followed by weekly for 4 weeks, and then monthly thereafter.
- If neutropenia were to develop post-LT, considerations may include discontinuing valganciclovir/valacyclovir and/or MMF, switching tacrolimus to cyclosporine, and initiating filgrastim prior to stopping clozapine.

Neuropsychiatric considerations

- Neuropsychiatric disturbances associated with corticosteroid therapy include affect and cognition changes, ranging from hypomania, euphoria, and irritability to delirium and psychosis.[3]
- Our patient likely experienced manic and psychotic symptoms as a result of his steroid use.
- The mainstay treatment for steroid-induced psychotic and manic symptoms is initiation of an antipsychotic or mood stabilizer.[3]
- We did not initially uptitrate his standing clozapine to stabilize his psychotic and manic symptoms due to the concern of synergistic effects of QT prolongation, hyperglycemia, lowering of seizure threshold with his post-LT medications (Table 1).
- We eventually increased clozapine dose with stabilization of his psychiatric symptoms and without adverse medical effects.

Conclusion

- Patients treated with clozapine require careful consideration in post-transplant management given the synergistic risk of medication-induced agranulocytosis in combination with immunosuppressant therapy and infection prophylaxis medications.
- Though limited, increasing evidence suggests that patients can be safely continued on clozapine through transplantation without adverse medical outcomes.

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