## 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 SOT without complications, such as psychotic decompensation, medication noncompliance, or graft loss.
- 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 immunosuppressant therapy and infection prophylaxis.
- 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.
- He had cirrhosis secondary to non-alcoholic steatohepatitis, as well as hypertension, hyperlipidemia, and diabetes mellitus.
- On postoperative day (POD) 7, the patient had hyperalgesia 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 up titrating 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

<table>
<thead>
<tr>
<th>Common LT Drugs</th>
<th>Indication</th>
<th>Clozapine Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Induction immunosuppression</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Maintenance immunosuppression</td>
<td>Agranulocytosis Seizures</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Maintenance immunosuppression</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Pneumocystis pneumonia prophylaxis</td>
<td>QT prolongation</td>
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<tr>
<td>Trimethoprim</td>
<td>Cyclophospholysis</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Fungal infection prophylaxis</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Flucytosine</td>
<td></td>
<td>QT prolongation</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Transplant Type</th>
<th>Psychotropic Medications</th>
<th>Transplant Medications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al. (2016), Asian Journal of Psychiatry</td>
<td>Renal</td>
<td>Clozapine 200mg daily</td>
<td>No specifics given</td>
<td>No synergistic side effects reported</td>
</tr>
<tr>
<td>Harrington et al. (2008), Psychopharmacology</td>
<td>Clozapine 350mg bid</td>
<td>Tacrolimus 20mg daily</td>
<td>No synergistic side effects reported</td>
<td></td>
</tr>
<tr>
<td>Wright et al. (2021), Psychoncology</td>
<td>Clozapine</td>
<td>Cyclophospholysis</td>
<td>WBCANC of 0 for 25 days, recovered on home clozapine dose</td>
<td></td>
</tr>
<tr>
<td>Burlingham et al. (2016), Progress in Neurology and Psychiatry</td>
<td>Clozapine 200/300mg</td>
<td>Methylprednisolone</td>
<td>WBCANC of 0, fully recovered despite home clozapine dose</td>
<td></td>
</tr>
<tr>
<td>Rosenberg et al. (2007), American Journal of Psychiatry</td>
<td>Lithium 1500mg daily</td>
<td>No specifics given</td>
<td>WBCANC of 0, fully recovered despite home clozapine dose</td>
<td></td>
</tr>
</tbody>
</table>

### References

2. Lim AM, Dhillon R, Tibrewal P, Bastiampillai T, Nguyen BDH. Clozapine, immunosuppressants and renal transplantation. 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.
4. The mainstay treatment for steroid-induced psychotic and manic symptoms is initiation of an antipsychotic or mood stabilizer.
5. We did not initially uptitrate his standing clozapine to stabilize his psychotic and manic symptoms due to concern of synergistic effects of QT prolongation, hyperglycemia, lowering of serum threshold with his post-LT medications (Table 1).
6. We eventually increased clozapine dose with stabilization of his psychiatric symptoms and without adverse medical effects.

### Discussion

- 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.
- There is evidence that patients can be safely continued on clozapine through transplantation without adverse medical outcomes.

### Conclusion

- Patients with psychotic disorders can successfully undergo SOT without complications, such as psychotic decompensation, medication noncompliance, or graft loss, with careful consideration of potential drug-drug interactions.
- Successful continuation of clozapine treatment during liver transplantation can be achieved with careful management of immunosuppression and infection prophylaxis medications.
- 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.

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**Successful Continuation of Clozapine Treatment During Liver Transplantation**

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**Common LT Drugs**

- **Corticosteroids**
- **Tacrolimus** (Calcineurin inhibitor)
- **Mycophenolate Mofetil** (Antiproiferative agent)
- **Sulfamethoxazole**/Trimethoprim
- **Valacyclovir**
- **Flucytosine**

**Indication**

- **Induction immunosuppression**
- **Maintenance immunosuppression**
- **Pneumocystis pneumonia prophylaxis**
- **Cyclophospholysis**
- **Fungal infection prophylaxis**

**Clozapine Interactions**

- **Hyperglycemia**
- **Agranulocytosis Seizures**
- **Agranulocytosis**
- **QT prolongation**
- **Agranulocytosis**
- **QT prolongation**

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