DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX –MANAGING PATIENTS ON SELECT PSYCHOTROPIC MEDICATIONS WITH MILD-MODERATE COVID-19 INFECTION TREATED WITH PAXLOVID®

CONTEXT:

Paxlovid® (nirmatrelvir tablets; ritonavir tablets) is one of several FDA-approved treatments for patients with mild-moderate COVID-19 infection. As a strong CYP3A4 inhibitor, ritonavir can cause a significant increase in plasma concentrations of certain psychotropic medications. By itself, COVID-19 infection can alter metabolism of clozapine resulting in elevated plasma levels.

ISSUES:

1. The impact of Paxlovid® on drug metabolism
2. The impact of mild-moderate COVID-19 infection on CYP1A2 activity and clozapine metabolism

I. Impact of Paxlovid® on drug metabolism

Paxlovid® is composed of two antiviral medications – nirmatrelvir and ritonavir. In terms of drug metabolism, only ritonavir is of interest as it is a strong CYP 3A4 inhibitor and has been used for over two decades to inhibit the metabolism of other antiviral agents in the context of HIV care.

- **Lurasidone** is metabolized by CYP 3A4. When lurasidone is administered with a strong CYP 3A4 inhibitor, the maximal plasma concentration is increased by 6.8-fold and the total drug exposure is increased by 9.3-fold. [1] This is a large increase in total drug exposure and places the patient at risk for side effects such as drug-induced parkinsonism, akathisia, and sedation. Those on lurasidone will need to have the drug held for the 5-day course of Paxlovid® treatment using the recommendations that follow.

- **Pimozide** is mainly metabolized by CYP 3A4 and to a lesser extent by CYP 1A2. Pimozide confers a higher risk than most antipsychotics of QTc prolongation.[2] Drugs that inhibit pimozide's metabolism will increase the risk of QT prolongation.

- **Clozapine** is primarily metabolized by CYP 1A2 and to a lesser extent by CYP 3A4 and CYP 2D6. The clozapine package insert does not provide specific guidance when using 2D6 or 3A4 inhibitors, stating, "Use caution and monitor patients closely when using such inhibitors." While ritonavir inhibits CYP 3A4, it also induces CYP 1A2 by 2.9-fold.[3] Overall, it may be unnecessary to reduce the clozapine dose unless the patient is exhibiting signs of clozapine toxicity, e.g., sedation, myoclonus, new/worsening sialorrhea, ataxia, etc. The clozapine package insert guidance appears appropriate in this context: use caution and monitor patients closely. Again, Paxlovid® is only a 5-day course of treatment so any effects may not be seen (if they occur at all) until the end of the antiviral treatment. (See below for complete recommendations.)

- **Quetiapine** is predominantly metabolized by CYP 3A4 and, to a lesser extent, 2D6. Per the package insert, "Quetiapine exposure is increased by the prototype CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc.) and decreased by the prototype CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, avasimibe, St.

John's wort etc.). Dose adjustment of quetiapine will be necessary if it is co-administered with potent CYP3A4 inducers or inhibitors." In a clinical study summarized in quetiapine prescribing information, coadministration of ketoconazole (200 mg daily for 4 days) increased the C_{max} and AUC of quetiapine (25 mg single dose) by 3.4-fold and 6.2-fold, respectively.[4] The dose of quetiapine should be reduced to one sixth of the original dose if co-administered with a strong CYP3A4 inhibitor and the quetiapine dose should be titrated up over 2 – 4 weeks to 6-fold following discontinuation of the strong CYP3A4 inhibitor.

- **Trazodone** is mainly metabolized by CYP 3A4 and, to a lesser extent, 2D6. In a pharmacokinetic study of 10 healthy volunteers, ritonavir (200 mg for 4 doses) increased the trazodone (50 mg single dose) AUC and C_{max} 2.4-fold and 1.3-fold, respectively. Increased side effects were noted when ritonavir was combined with trazodone, including sedation, fatigue, hypotension, syncope, and performance impairment.[5]

II. Impact of covid-19 infection on enzyme activity and drug metabolism

Briefly, COVID-19 infection appears to impact hepatic enzymes (CYP P450 isoforms) involved in drug metabolism, primarily CYP 1A2. During acute infections, inflammatory cytokines such as IL-6 are produced and downregulate CYP 1A2 production. Clozapine is the antipsychotic most affected by COVID-19 infection since it is so heavily dependent on 1A2 metabolism. The net result is elevation of the clozapine plasma level 3-4 fold during acute severe infections such as COVID-19. Olanzapine has dual pathways through 1A2 and a phase 2 enzyme, and the impact on its clearance is not as significant when 1A2 is inhibited or downregulated.

Significant elevation of clozapine plasma levels has also been observed in patients who are asymptomatic or have only mild signs/symptoms of COVID-19 infection. While impairment of hepatic metabolism and elevation of medication plasma concentrations generally correlate with severity of infections, this is only a correlation. There may be atypical cases of elevated plasma levels that do not correlate with COVID-19 symptom presentation. Hence, significant elevation of clozapine could occur in patients who have mild signs/symptoms of COVID-19 infection or are seemingly asymptomatic.

In general, our recommendation for patients who have tested positive for COVID-19 but have minimal or mild symptoms is to monitor the patient over the next 1-2 weeks for signs of clozapine toxicity.

If any signs of toxicity are present:

- Recheck the plasma clozapine level
- Lower the daily clozapine dose by 25% to 50%
- Recheck the plasma clozapine level 5 days after the dose decrease
- When the infection has abated, re-titrate the clozapine to the former dose[6]

PRN Recommendations when patients on lurasidone, pimozide, clozapine, quetiapine, and/or trazodone develop mild-moderate COVID-19 infection and are treated with Paxlovid®:

1. Lurasidone and pimozide patients: Twelve to 24 hours prior to starting Paxlovid®, stop lurasidone or pimozide. On Day 4 of Paxlovid® treatment, restart lurasidone or pimozide at ½ the previous dose and titrate to the previous dose over the next week.

2. Clozapine patients: Clozapine patients should already be monitored s/p positive COVID-19 test for the development of any signs of clozapine toxicity. Since Paxlovid® has mixed effects on clozapine metabolism, continue the dose of clozapine as is and monitoring for signs of clozapine toxicity. If any signs of toxicity are present:

    a. Recheck the plasma clozapine level

    b. Lower the daily clozapine dose by 25% to 50%

    c. On the day after completing treatment with Paxlovid® and provided that there are no signs of toxicity, re-titrate the clozapine to the previous dose if dose reduction was necessary.

3. Quetiapine patients: The principal risks of a Paxlovid®-induced decrease in quetiapine metabolism would be excessive sedation and/or orthostatic hypotension. At low doses (e.g., for sedation), this adverse effect would be unlikely. At higher doses (antidepressant and antipsychotic dosages), it could become significant 24 – 48 hours following initiation of Paxlovid®.

    a. If the dosage of quetiapine is ≤100 mg, no changes need to be made.

    b. If the dosage of quetiapine >100 mg, consider tapering the dosage by 50 – 75% on initiation of Paxlovid®.

    c. On the day after completing treatment with Paxlovid® and provided that there are no signs of toxicity, re-titrate quetiapine to the previous dose if dose reduction was necessary.

4. Trazodone patients: An alternative sedative would be hydroxyzine which is not metabolized by either CYP1A2 or CYP3A4.

    a. If trazodone is continued, decrease the dose by 50 – 75% on initiation of Paxlovid®.

    b. On the day after completing treatment with Paxlovid® and provided that there are no signs of toxicity, re-titrate trazodone to the previous dose if dose reduction was necessary.

Other Potentially Significant Psychotropic Drug Interactions when Treating with a 5-Day Course of Paxlovid®

Co-administration of Paxlovid® with drugs that are primarily metabolized by CYP 3A and CYP 2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of these drugs and increase the risk of adverse events. Conversely, since nirmatrelvir and ritonavir are CYP 3A substrates, drugs that induce CYP 3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce Paxlovid's® therapeutic effect.

Other Potentially Significant Psychotropic Drug Interactions with Paxlovid®[7]

Drug Class	Drugs within Class	Effect on Drug Concentration	Clinical Comments
Anticonvulsants	Carbamazepine	↓ nirmatrelvir/ritonavir	Co-administration is contraindicated due to potential loss of virological response and possible resistance
Antidepressants	Bupropion	↓ bupropion and active metabolite, hydroxybupropion	Monitor for adequate clinical response to bupropion. See above for discussion on trazodone
Antipsychotics	Aripiprazole Brexpiprazole Cariprazine Iloperidone Lumateperone Pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Reduce antipsychotic dose and monitor for adverse reactions. See above for discussion on clozapine, lurasidone, quetiapine, and pimozide
Sedative hypnotics	Clonazepam Diazepam Zolpidem	↑ sedative/hypnotic	Consider a dose decrease when co-administered with Paxlovid®
Other	Buspirone	↑ buspirone	Consider a dose decrease when co-administered with Paxlovid®

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