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FROM: Dr. Thomas Smith, Chief Medical Officer
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DATE: January 12, 2022

SUBJECT: Clinical Advisory on Paxlovid Treatment for COVID-19 Positive and Symptomatic Patients Currently on Clozapine

Before administering Paxlovid to patients who are receiving clozapine and have symptomatic COVID-19, consider the risk factors and information provided below.

Considerations prior to initiating COVID-19 anti-viral treatment in patients on clozapine

- The monoclonal antibody Sotrovimab is highly effective in reducing hospitalization rates and should be considered a suitable alternative treatment modality if locally available.
- Other considerations include a patient's vaccination status (whether fully vaccinated and received a booster vaccine within the last ten weeks), other comorbid conditions, and age.
- If Paxlovid (nirmatrelvir and ritonavir combination product) is co-administered with clozapine in a stabilized patient, therapeutic drug monitoring (TDM) practices are critical to ensure that plasma clozapine concentrations are maintained within therapeutic range. This is due to the well-documented drug interactions between ritonavir (a component of Paxlovid) and clozapine. **Specifically, Paxlovid administration could increase plasma concentrations of clozapine in a stable patient due to ritonavir's and nirmatrelvir's inhibition of CYP3A4 metabolic enzymes**. *(FDA 2021)* The effect of nirmatrelvir alone on clozapine plasma concentration has not been studied and is currently unknown. *(Liverpool)* Paxlovid dosing requires a dose to be administered twice daily for five days. *(FDA 2021)*
- Clinicians should also keep in mind that respiratory tract infections, including COVID-19, may cause increased clozapine serum levels, especially when there are systemic manifestations of fever with C-reactive protein elevations and a significant cytokine release. Clinicians should consider decreasing clozapine doses when patients are diagnosed with COVID-19, regardless of considerations related to drug-drug interactions. For further information, see: Siskind D, J Psychiatry Neurosci. 2020 Apr 3.

Starting a clozapine patient on Paxlovid

Basic pharmacokinetic (PK) attributes of clozapine, ritonavir, and nirmatrelvir (with co-administration of ritonavir) need to be understood to develop TDM protocols for clozapine when initiating Paxlovid:

Ritonavir *– Relevant PK Attributes (FDA 2021)*
Metabolic Pathways: CYP3A4 (Major), CYP2D6 (Minor)
Time to Peak (Median): 3.98 hours
Half-Life Elimination (Mean): 6.15 hours

Nirmatrelvir *(when given with Ritonavir) – Relevant PK Attributes (FDA 2021)*
Metabolic Pathways: Minimal. Nirmatrelvir is a CYP3A4 substrate, but when dosed with ritonavir, metabolic clearance is minimal.
Time to Peak (Median): 3.00 hours
Half-Life Elimination (Mean): 6.05 hours

Clozapine *– Relevant PK Attributes (HLS Therapeutics 2020)*
Metabolic Pathways: CYP1A2 (Major), CYP3A4 (Major), CYP2D6 (Minor)
Time to Peak (Median): 2.5 hours
Half-Life Elimination at Steady State (Mean): 12 hours

The 2017 update to the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology recommends that when co-administering products with known drug-drug interactions, **TDM should guide dosing to avoid loss of action, poor tolerability, or toxicity due to the noted PK drug-drug interaction**. These guidelines also note that trough sampling, performed just prior to administration of a patient's dose, to obtain plasma concentrations of clozapine is practical and clinically informative. *(Hiemke, C. et al.)*

Ideal TDM practices to monitor clozapine plasma concentrations in the setting of Paxlovid co-administration

- Obtain clozapine plasma concentrations immediately prior to the first dose of Paxlovid, which should be given at the same time as the scheduled dose of clozapine. Obtaining a clozapine plasma concentration prior to initiating Paxlovid in this way ensures an accurate baseline concentration is obtained. *A Paxlovid regimen should not be initiated if a patient displays signs and/or symptoms of clozapine toxicity or high clozapine plasma levels.*
- After the first dose of Paxlovid is administered, a repeat clozapine trough concentration should be obtained before the next administered dose of clozapine (and Paxlovid, assuming they are given simultaneously).
- Given the required time for the return of the plasma level result (typically 24 hours or more) and the need to not interrupt the co-administration of Paxlovid and clozapine, we recommend a clozapine dose reduction of 1/3 for the next dose until results of the TDM are available, together with close monitoring of toxic clozapine side effects such as oversedation and vital sign changes.
- Once the results are available, the change in clozapine plasma level (before and after Paxlovid first dose) should be reviewed, and an adjustment of the dose should be made with the goal to stay below the upper level of the range of therapeutic clozapine plasma level. Consider repeating the same TDM procedure after the new dose adjustment of clozapine has been initiated. Remember that the effect of dose changes for clozapine

will not be seen immediately as the half-life elimination at steady state of clozapine is 12 hours.

- Once the Paxlovid regimen is completed, a clozapine trough level should be obtained to maintain TDM while the components of Paxlovid are being cleared from the body (half-life elimination 6.15 and 6.05, respectively). Once results are available, the dose may be increased again to reach a therapeutic plasma level.
    - This recommendation is based on the elimination half-life of each component of about 6 hours on average and the need for 5 half-lives (in this case, 30 hours) to pass for a drug to be 95% eliminated.

References

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The University of Liverpool [Internet]. Liverpool: The University of Liverpool; c2022 [cited 2022 Jan 6]. Available from: https://www.covid19-druginteractions.org/checker.

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