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# Ritonavir/Lopinavir and Its Potential Interactions With Psychiatric Medications: A COVID-19 Perspective

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The coronavirus disease 2019 (COVID-19) pandemic is a global catastrophe. One of the medications being proposed for the treatment of COVID-19 is the antiretroviral drug combination of ritonavir and lopinavir.<sup>1</sup> Ritonavir is a potent cytochrome P450 (CYP) 2D6, 3A4, and 1A2 inhibitor and a CYP2B6, CYP2C19, and glucuronidation inducer.<sup>1</sup> It is also an inducer and inhibitor of p-glycoprotein (a transmembrane drug efflux pump that extrudes toxins and hence protects organs).<sup>2</sup> It is also a CYP2D6 and CYP3A4 substrate. CYP inhibition of ritonavir rises with increased dose, and it affects CYP2D6 more than other CYP enzymes. Lopinavir is primarily metabolized by CYP3A4. Lopinavir, when combined with a low dose of ritonavir, inhibits its own metabolism and thus augments its effect.<sup>3</sup> Psychotropics are metabolized by the CYP enzymes and have a multitude of drug interactions with this antiretroviral combination.<sup>1</sup>

## Antidepressants

**Selective serotonin reuptake inhibitors.** Citalopram and escitalopram are substrates of CYP2C19 and CYP3A4 and also weakly inhibit and are a substrate of CYP2D6. However, escitalopram combined with ritonavir was not found to produce clinically relevant changes.<sup>4,5</sup> Escitalopram and citalopram are metabolized through multiple different pathways and so have less propensity for interactions. Thus, escitalopram and citalopram are preferred over other antidepressants due to minimal interactions with ritonavir.<sup>1,6</sup>

Fluoxetine is predominantly metabolized through CYP2D6 and CYP3A4. It also has inhibitory effects on

CYP2D6, CYP2C9, CYP2C19, and CYP3A4, with the most potent effect on CYP2D6. When coadministered with a high dose of ritonavir (400–1200 mg), fluoxetine has been reported to cause serotonin syndrome or serotonin toxicity and should be used with caution.<sup>1,6,7</sup>

Fluvoxamine is metabolized through CYP2D6 and CYP1A2 and has potent inhibitory effects on CYP1A2 and CYP2C19, moderate inhibitory effects on CYP2C9 and CYP3A4, and weak inhibitory effects on CYP2D6. When coadministered with protease inhibitors (PIs), the concentration of the PIs could potentially increase or decrease given the effects on multiple CYP enzymes, so another antidepressant drug is recommended.<sup>6</sup>

**Serotonin-norepinephrine reuptake inhibitors.** Venlafaxine is a substrate and weak inhibitor of CYP3A4 and CYP2D6, as is desvenlafaxine. There is a paucity of literature regarding venlafaxine coadministered with ritonavir or lopinavir. It is recommended that extended-release formulations of venlafaxine and desvenlafaxine be used if the benefits exceed the risks, as research on venlafaxine with indinavir, a similar drug, showed the same results.<sup>1,6</sup>

Duloxetine is metabolized by CYP2D6 and CYP1A2. When combined with a potent CYP2D6 or CYP1A2 inhibitor, duloxetine's concentrations increased significantly.<sup>3,6</sup>

Paroxetine, a CYP2D6 inhibitor, increases the concentration of duloxetine by 60%, and CYP1A2 inhibitors increase the level of duloxetine by 6-fold.<sup>6</sup> Such interaction could be possible with other potent CYP2D6 inhibitors such as ritonavir. Ritonavir in a dose of 200 mg twice/day when coadministered with duloxetine has caused adverse effects such as sedation, fatigue, hypotension, and syncope potentially due to increased levels.<sup>6</sup> For this reason, an alternative antidepressant should be considered when coadministered with ritonavir.<sup>6</sup>

Milnacipran and levomilnacipran are metabolized minimally by CYP3A4 and require dose reduction when coadministered with potent CYP3A4 inhibitors like ritonavir.<sup>1,6</sup> However, literature regarding these interactions is sparse.

**Tricyclic antidepressants.** These antidepressants are substrates of CYP3A4 and CYP2D6. When tricyclic antidepressants are used with a CYP2D6 inhibitor such as ritonavir, close monitoring is recommended.<sup>1</sup>

**Monoamine oxidase inhibitors.** Monoamine oxidase inhibitors do not potentially interact with ritonavir with regard to CYP enzymes. However, we do not recommend

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using a monoamine oxidase inhibitor with ritonavir due to its narrow therapeutic index and potential cardiac side effects.<sup>1</sup>

**Miscellaneous.** Trazodone is metabolized by CYP2D6 and CYP3A4. The levels of trazodone can be significantly increased when used with ritonavir, theoretically up to 240%, with an increase in side effects such as sedation, hypotension, and syncope.<sup>1,6</sup> If trazodone is indicated, it should be started at a low dose and monitored for adverse effects.

Mirtazapine is metabolized by CYP1A2, CYP3A4, and CYP2D6 with no appreciable inhibitory or inducing properties.<sup>1,3,6</sup> There are no well-delineated drug interactions between mirtazapine and antiretrovirals.

Bupropion is a substrate of CYP2B6. When coadministered with ritonavir/lopinavir combination, bupropion's area under the curve (AUC) decreased by 57%.<sup>6</sup> When combined, a higher dose of up to 100% of the dose may be required.<sup>1,6</sup> Also, as the dose of ritonavir increases, the bupropion dose should be proportionately increased.

Vortioxetine and vilazodone have a weak to no inhibitory effect on CYP enzymes and display no drug interactions.<sup>6</sup> Literature is scarce with regard to vortioxetine and vilazodone with ritonavir.

**Antipsychotics.** Aripiprazole is a substrate of CYP3A4 and CYP2D6, and its level can be increased when combined with inhibitors of these enzymes such as ritonavir. When coadministered, aripiprazole should be started at a low dose.<sup>1,6</sup> There is sparse literature on the drug interactions between ritonavir and aripiprazole.

Olanzapine is metabolized by CYP1A2 and UGT (UDP-glucuronosyltransferase) 1A4 enzymes. An open-label crossover study<sup>8</sup> showed a 53% decrease in the olanzapine AUC when coadministered with ritonavir (300–500 mg twice/day).<sup>1,6</sup> If combined with ritonavir-containing antiretroviral therapy, a 50% increase in the dose of olanzapine would be necessary.<sup>6</sup>

Quetiapine is metabolized by CYP3A4. When quetiapine was coadministered with ritonavir and atazanavir, there was a 50-lb increase in weight and hyperglycemia.<sup>6</sup> A case report<sup>9</sup> described mental confusion and sedation when quetiapine was combined with the same antiretroviral combination. Another case report<sup>10</sup> described a patient who experienced priapism as a result of drug interactions between ritonavir and quetiapine. When a protease inhibitor such as ritonavir is added to a stable dose of quetiapine, the antipsychotic dose should be reduced to one-sixth of its original.<sup>6</sup> When quetiapine is added to ritonavir, the lowest possible dose of quetiapine should be used and titrated upward.<sup>6</sup>

Risperidone is a substrate of CYP2D6 and CYP3A4. Combining ritonavir with risperidone has been shown to increase side effects such as extrapyramidal symptoms, neuroleptic malignant syndrome, altered mental status, and coma.<sup>1,6</sup> Angioedema has also been reported due to drug interactions between ritonavir and risperidone.<sup>11</sup>

Lurasidone is metabolized by CYP3A4.<sup>1</sup> It is contraindicated when combined with ritonavir due to an increase in lurasidone concentration.<sup>6</sup>

Ziprasidone has a high risk of prolonging the QTc interval.<sup>1</sup> If coadministered with ritonavir and lopinavir, ziprasidone could potentially have an additive effect and prolong the QTc interval. Such prolonged QTc intervals can lead to life-threatening ventricular arrhythmias, torsades de pointes, and sudden cardiac death.<sup>3</sup>

**Mood stabilizers.** Carbamazepine is an inducer of CYP3A4 and CYP1A2, as well as a substrate of CYP1A2. Coadministration with ritonavir has led to an increase in blood levels of carbamazepine to toxic concentrations, causing blood dyscrasia, cardiovascular instability, ocular abnormalities, neurologic deficits, and dermatologic reactions. Carbamazepine should not be coadministered with lopinavir/ritonavir combination due to a potential increase in the concentration of the mood stabilizer.<sup>6</sup>

Sodium valproate is metabolized by CYP2C9, CYP2B6, and CYP2A6.<sup>12</sup> When combined with lopinavir/ritonavir, valproate caused a decrease in the concentration of the mood stabilizer, leading to the development of symptoms of mania and hypomania. However, data on coadministering these drugs are inconclusive, and caution is advised when using the combination.<sup>6</sup>

Lamotrigine is mainly metabolized via glucuronidation.<sup>13</sup> When coadministered with ritonavir/lopinavir combination, its AUC decreases by 50%.<sup>6</sup> With this combination, a higher dose of lamotrigine may be necessary.

Lithium is not metabolized and eliminated directly through the kidney.<sup>14</sup> There is limited literature regarding its interaction with lopinavir/ritonavir, and the propensity for interactions is very low.

**Anxiolytics.** Buspirone is a CYP3A4 substrate. In a case report,<sup>15</sup> when buspirone was combined with ritonavir-containing antiretroviral therapy, the patient developed parkinsonian symptoms.<sup>1,6</sup> Caution is advised when using this combination.

Midazolam is metabolized by CYP3A4. Coadministration of midazolam with ritonavir caused an increase in midazolam concentration.<sup>6</sup>

CYP3A4 and CYP2C19 metabolize diazepam. When combined with ritonavir, the effects of diazepam may be prolonged. HIV treatment guidelines<sup>6</sup> have suggested avoiding this combination. The same holds true for triazolam, which is metabolized through CYP3A4.<sup>6</sup>

Alprazolam is metabolized by CYP3A4. There is contradicting literature on the coadministration of alprazolam with ritonavir. While 1 case report described no effects, another described sedation and psychomotor retardation.<sup>16</sup> Therefore, it is advised to start alprazolam at a low dose and closely monitor the patient.<sup>6</sup>

If benzodiazepines are indicated, lorazepam, temazepam, or oxazepam should be chosen over alprazolam, as these drugs do not undergo hepatic metabolism.<sup>6</sup>

**Stimulants.** Amphetamines are metabolized by oxidation, deamination, and CYP2D6. When combined with ritonavir, an inhibitor of CYP2D6 could potentially increase the levels of amphetamines. In vitro studies<sup>17</sup> of methylphenidate indicate that it may inhibit CYP2D6 and CYP2B6. There

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**Table 1. Significant Psychotropic Drug-Drug Interactions With Ritonavir/Lopinavir**

Drug	Combined With	Mechanism of Interaction	Outcome
Fluoxetine	Ritonavir and other antiretroviral	Fluoxetine is a cytochrome P450 (CYP) 2D6 substrate; ritonavir is a potent CYP2D6 inhibitor	Serotonin syndrome or toxicity
Sertraline and paroxetine	Ritonavir with other protease inhibitors	Sertraline and paroxetine are CYP2D6 inhibitors; ritonavir is a potent CYP2D6 inhibitor	Decrease concentration of antidepressant by 39%–55%
Trazodone	Ritonavir	Trazodone is a CYP2A4 and CYP2D6 substrate; ritonavir is a potent CYP2D6 and CYP3A4 inhibitor	240% increase in area under the curve of trazodone causing adverse effects such as sedation, fatigue, hypotension, and syncope
Bupropion	Lopinavir/ritonavir combination	Bupropion is a CYP2B6 substrate; ritonavir is a CYP2B6 inducer	Decrease in bupropion concentration by 57%; up to 100% increase in dose may be required
Olanzapine	Ritonavir	Olanzapine is a CYP1A2 and UGT1A4 substrate; ritonavir is a CYP1A2 and glucuronidation inducer	53% decrease in olanzapine area under the curve
Quetiapine	Atazanavir or ritonavir	Quetiapine is a CYP3A4 substrate; ritonavir is a CYP3A4 inhibitor	Adverse effects such as weight gain, mental confusion, and priapism; use one-sixth of the dose when starting quetiapine
Risperidone	Ritonavir or indinavir	Risperidone is a CYP2D6 and CYP3A4 substrate; ritonavir is a CYP2D6 and CYP3A4 inhibitor	Adverse effects such as extrapyramidal symptoms, altered mental status, neuroleptic malignant syndrome, and angioedema
Carbamazepine	Ritonavir	Carbamazepine is a substrate and inducer of CYP1A2 and CYP3A4; ritonavir is a CYP1A2 and CYP3A4 inhibitor	Toxic levels of carbamazepine leading to blood dyscrasia, cardiovascular instability, ocular abnormalities, neuro deficits, and dermatologic reactions

Abbreviation: UGT = UDP-glucuronosyltransferase.

are sparse data on interactions of stimulants with ritonavir. The clinical significance of these in vitro data is unknown. It is recommended to begin at a low dose when starting these medications.<sup>6</sup> Dexmethylphenidate and lisdexamfetamine do not interact with CYP and are considered better options when necessary.<sup>6</sup>

In summary, these significant drug interactions (Table 1) should be kept in mind before starting psychotropics in a patient on ritonavir/lopinavir combination therapy for COVID-19. When coadministered, the precautions mentioned here should be taken due to the high propensity for interactions.

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