Benzodiazepine Interaction With COVID-19 Drugs

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The coronavirus disease 2019 (COVID-19) pandemic has adversely impacted social, financial, and health care aspects of people's lives globally.[1-4] It has led to an increase in anxiety, panic attacks, and insomnia, causing an increase in the use of benzodiazepines.[2,3,5,6] Benzodiazepines are one of the most commonly prescribed medications for anxiety, insomnia, and epilepsy.[5] According to the US Food and Drug Administration (FDA), in 2019 about 92 million benzodiazepine prescriptions were dispensed in the United States.[5] About 5 million US adults have reported misuse of benzodiazepines out of a total of 30 million users.[7] Abuse and misuse of benzodiazepines have caused a higher volume of emergency department visits, especially with the concurrent use of other substances and prescribed medications.[8] At the same time, several medications are being used to manage and treat COVID-19 patients.[9] However, limited evidence has been brought to light thus far regarding the interaction of these drugs with benzodiazepines, their mechanisms of action, and the outcomes of these interactions when utilized in humans. Since the drug-to-drug interaction with clinical significance was only found between the antiviral class of drugs for COVID-19 and benzodiazepines, we reviewed the potential drug-to-drug interactions and safety of using benzodiazepines with COVID-19 antiviral drugs.[9]

One such antiretroviral treatment is the combination of ritonavir and lopinavir. Ritonavir is a potent cytochrome P450 (CYP) 2D6, 3A4, and 1A2 inhibitor and a CYP2B6 and CYP2C19 glucuronidation inducer.[10] On the other hand, lopinavir is metabolized by CYP3A4. Since the cytochrome system also metabolizes benzodiazepines, combining it with a low dose of ritonavir and lopinavir facilitates the inhibition of its metabolism and exaggerates its effects.[10]

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Drug-To-Drug Interactions of Benzodiazepines and COVID-19 Antivirals

Midazolam (oral) is a benzodiazepine metabolized by CYP3A4.[10] Coadministration of midazolam with a CYP3A4 inhibitor, such as ritonavir, may promote increased midazolam concentration.[9,10] Outcomes of this interaction are disruptions such as increased confusion, respiratory depression, and sedation due to increased plasma concentrations of midazolam.[9] Therefore, this combination is highly contraindicated for coadministration.[9]

Atazanavir is another CYP3A4 inhibitor, and its concurrent use with oral midazolam facilitates possible severe events such as prolonged sedation, increased confusion, and respiratory depression.[9] The combined use of atazanavir with oral midazolam is contraindicated due to their potential adverse interaction. The combination of parenteral midazolam with atazanavir should be applied cautiously, with close clinical monitoring and dose and administration interval alternation to avoid respiratory depression. Reducing midazolam's dose has also been recommended.[9]

Triazolam is widely regarded as a drug for the treatment of insomnia.[11] It is also considered a central nervous system (CNS) depressant tranquilizer, which increases the triazolam effects such as sedation, confusion, and respiratory depression when combined with atazanavir.[9] Furthermore, with ritonavir being a CYP3A4 inhibitor, its concomitant use with triazolam causes a similar effect as the triazolam-atazanavir combination and is not recommended.[9]

Alprazolam is metabolized by CYP3A4, and coadministration with atazanavir results in a possibility of enhanced sedation.[9] It is recommended that doses of alprazolam be reduced to prevent the undesirable effects of the combination. In addition, alprazolam plus ritonavir can cause inhibition of alprazolam metabolism without noticeable inhibitory effects in its steady state.[9] While there are contrasting results, studies consistent with these findings also found psychomotor retardation to be an effect of the combination.[12]

Chlordiazepoxide is commonly utilized to treat minor mental illnesses.[13] It is extensively metabolized by the hepatic microsomal enzymes. The combined use of chlordiazepoxide with atazanavir or ritonavir can enhance its activity, posing a greater risk of adverse effects such as sedation, memory impairment, ataxia, and respiratory depression.[9]

Clobazam is effective for the management of generalized seizures.[14] It is metabolized by CYP3A4, CYP2B6, and CYP2C19.[9] Use of clobazam with ritonavir increases the

Table 1. COVID-19 Drug Interaction With Benzodiazepines

#	Benzodiazepines	COVID-19 Drugs	Level of Interaction	Absolutely Contraindicated	Additional Monitoring Required	Drug Dosage Alteration Required	Drug Timing Alteration Required	Mechanism of Interaction	Outcome
Strong interaction contraindicates coadministration of drugs									
1	Midazolam (oral)	Atazanavir	+++	Yes	NA	NA	NA	Midazolam is metabolized by CYP3A4; atazanavir inhibits CYP3A4	Increased midazolam effects such as increased confusion, respiratory depression, and sedation
2	Midazolam (oral)	Lopinavir/ ritonavir	+++	Yes	NA	NA	NA	Midazolam is metabolized by CYP3A4; ritonavir inhibits CYP3A4	Increased plasma concentration of midazolam causing disruptions such as increased confusion, respiratory depression, and sedation
3	Triazolam	Atazanavir	+++	Yes	NA	NA	NA	Triazolam is a CNS depressant tranquilizer; atazanavir inhibits CYP3A4	Increased triazolam effects such as sedation, confusion, and respiratory depression
4	Triazolam	Lopinavir/ ritonavir	+++	Yes	NA	NA	NA	Triazolam is a CNS depressant tranquilizer; ritonavir inhibits CYP3A4	Increased triazolam effects such as sedation, confusion, and respiratory depression
Significant interaction requires additional caution									
5	Alprazolam	Atazanavir	++	No	Yes	Yes	Yes	Alprazolam is metabolized by CYP3A4; atazanavir inhibits CYP3A4	Enhanced sedation
6	Alprazolam	Lopinavir/ ritonavir	++	No	Yes	Yes	Yes	Alprazolam is metabolized by CYP3A4; ritonavir inhibits CYP4503A4	Inhibition of alprazolam metabolism following the introduction of ritonavir but no significant inhibitory effect at steady state
7	Chlordiazepoxide	Atazanavir	++	No	Yes	Yes	Yes	Chlordiazepoxide is extensively metabolized by hepatic microsomal enzymes; atazanavir inhibits CYP3A4	Activities of chlordiazepoxide enhanced
8	Chlordiazepoxide	Lopinavir/ ritonavir	++	No	Yes	Yes	Yes	Chlordiazepoxide is extensively metabolized by hepatic microsomal enzymes; ritonavir inhibits CYP3A4	The activity of chlordiazepoxide may be increased
9	Clobazam	Lopinavir/ ritonavir	++	No	Yes	Yes	Yes	Clobazam is metabolized by CYP3A4 (major) and CYP2B6 and CYP2C19 (minor) to the active metabolite *N*-desmethylclobazam, which is metabolized by CYP2C19; ritonavir inhibits CYP3A4	CYP3A4 inhibition by lopinavir/ritonavir may increase clobazam exposure and prolong the duration of its effect, whereas induction of CYP2C19 by ritonavir may decrease *N*-desmethylclobazam
10	Clorazepate	Atazanavir	++	No	Yes	Yes	Yes	Clorazepate is rapidly converted to nordiazepam, which is then metabolized to oxazepam by CYP3A4; atazanavir inhibits CYP3A4	Atazanavir could potentially increase nordiazepam exposure, which could prolong sedation
11	Clorazepate	Lopinavir/ ritonavir	++	No	Yes	Yes	Yes	Clorazepate is rapidly converted to nordiazepam, which is then metabolized to oxazepam by CYP3A4; ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase nordiazepam exposure, which could prolong sedation
12	Diazepam	Atazanavir	++	No	Yes	Yes	Yes	Diazepam is metabolized to nordiazepam (by CYP3A4 and 2C19) and temazepam (mainly by CYP3A4); atazanavir inhibits CYP3A4	Atazanavir could potentially increase diazepam exposure by inhibition of CYP3A4; this could prolong sedation, and a dosage reduction may be required
13	Diazepam	Lopinavir/ ritonavir	++	No	Yes	Yes	Yes	Diazepam is metabolized to nordiazepam (by CYP3A4 and 2C19) and to temazepam (mainly by CYP3A4); ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase diazepam exposure by inhibition of CYP3A4; this could prolong sedation, and a dosage reduction may be required
14	Estazolam	Atazanavir	++	No	Yes	Yes	Yes	Estazolam is metabolized to its major metabolite 4-hydroxyestazolam via CYP3A4; atazanavir inhibits CYP3A4	Atazanavir could potentially increase estazolam exposure; this could prolong sedation, and a dosage reduction may be required

(continued)

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Table 1 (continued).

#	Benzodiazepines	COVID-19 Drugs	Level of Interaction	Absolutely Contraindicated	Additional Monitoring Required	Drug Dosage Alteration Required	Drug Timing Alteration Required	Mechanism of Interaction	Outcome
Significant interaction requires additional caution									
15	Estazolam	Lopinavir/ritonavir	++	No	Yes	Yes	Yes	Estazolam is metabolized to its major metabolite 4-hydroxyestazolam via CYP3A4; ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase estazolam exposure; this could prolong sedation, and a dosage reduction may be required
16	Flunitrazepam	Atazanavir	++	No	Yes	Yes	Yes	Flunitrazepam is metabolized mainly via CYP3A4 and CYP2C19; atazanavir inhibits CYP3A4	Atazanavir could potentially increase flunitrazepam exposure, which could result in increased sedation or respiratory sedation
17	Flunitrazepam	Lopinavir/ritonavir	++	No	Yes	Yes	Yes	Flunitrazepam is metabolized mainly via CYP3A4 and CYP2C19; ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase flunitrazepam exposure, which could result in increased sedation or respiratory sedation
18	Flurazepam	Atazanavir	++	No	Yes	Yes	Yes	The metabolism of flurazepam is most likely CYP-mediated; atazanavir inhibits CYP3A4	Atazanavir could potentially increase flurazepam exposure, which could result in increased sedation or respiratory sedation
19	Flurazepam	Lopinavir/ritonavir	++	No	Yes	Yes	Yes	The metabolism of flurazepam is most likely CYP-mediated; ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase flurazepam exposure, which could result in increased sedation or respiratory sedation
20	Midazolam (parenteral)	Atazanavir	++	No	Yes	Yes	Yes	Midazolam is metabolized by CYP3A4; atazanavir inhibits CYP3A4	Possibility of sedation and/or respiratory depression
21	Midazolam (parenteral)	Lopinavir/ritonavir	++	No	Yes	Yes	Yes	Midazolam is metabolized by CYP3A4; ritonavir inhibits CYP3A4	Possibility of prolonged sedation and/or respiratory depression
Weak interaction									
22	Bromazepam	Atazanavir	+	No	No	No	No	CYP3A4 plays a minor role in bromazepam metabolism, but other cytochromes such as CYP2D6 or CYP1A2 may play a role; atazanavir inhibits CYP3A4	Atazanavir could potentially increase bromazepam concentrations, although to a moderate extent
23	Bromazepam	Lopinavir/ritonavir	+	No	No	No	No	CYP3A4 plays a minor role in bromazepam metabolism, but other cytochromes such as CYP2D6 or CYP1A2 may play a role; ritonavir inhibits CYP3A4	Lopinavir/ritonavir could potentially increase bromazepam concentrations, although to a moderate extent

Abbreviations: CNS = central nervous system, COVID-19 = coronavirus disease 2019, CYP = cytochrome P450.
Symbols: + = weak interaction, ++ = significant interaction, +++ = strong interaction.

exposure of clobazam and prolongs the duration of its effects and hence requires constant monitoring for side effects by a clinician.[2,9]

Clorazepate is used as an anticonvulsant and anxiolytic to manage and treat epilepsy, anxiety, and alcohol abuse.[15] Clorazepate is rapidly converted to nordiazepam and, in turn, is metabolized to oxazepam by CYP3A4. Its interaction with a CYP3A4 inhibitor such as atazanavir or ritonavir could increase clorazepate's concentration and lead to prolonged sedation.[9] Thus, dose reduction may be required.[9,15]

Diazepam is used to manage seizures in prehospital settings.[16] Diazepam is metabolized by CYP3A4 and CYP2C19 to nordiazepam and tamazepam.[9,10] When diazepam is combined with ritonavir or atazanavir, its effects may be prolonged.[10] The University of Liverpool reported similar findings—that concurrent administration of diazepam with ritonavir or atazanavir could lead to prolonged sedation, likely requiring dosage reduction.[9]

Estazolam is used in the management and treatment of insomnia.[17] It is metabolized to its primary metabolite 4-hydroxyl estazolam through CYP3A4.[9] The coadministration of estazolam and CYP3A4 inhibitors atazanavir or ritonavir could potentially lead to more exposure and thereby prolonged sedation.[9] It is recommended that there should be a dosage reduction to alleviate these effects.

Flunitrazepam is used as a preanesthetic agent and a sedative in the treatment of insomnia.[18] It is mainly metabolized through CYP3A4 and CYP2C19.[9] Combining flunitrazepam with CYP3A4 inhibitors such as atazanavir and ritonavir can increase its exposure, leading to respiratory sedation.[9] A dosage reduction is recommended.

Flurazepam is widely used to manage sleep disorders.[19] Its metabolism is CYP-mediated. Though not studied, its combination with CYP3A4 inhibitors could increase respiratory sedation, and a dosage reduction is recommended.[9]

Bromazepam exhibits anxiolytic properties and is used for anxiety disorders.[20] Metabolism of bromazepam is carried out by CYP3A4 (minor) and CYP2D6 or CYP1A2. Bromazepam's concentration may moderately increase with concurrent use of CYP3A4 inhibitors (atazanavir and ritonavir). Since the drug-to-drug interactions are potentially weak, additional actions and close monitoring are not suggested.[9] Further details are provided in Table 1.[5,6,9,10,13,14,18-20]

In conclusion, benzodiazepines have shown significant levels of interaction with COVID-19 drugs. When benzodiazepines are indicated, it is better to use temazepam, oxazepam, or lorazepam over alprazolam, as the liver does not metabolize them.[1] There is also a need for further research to evaluate the safety of adjunct therapy. Since benzodiazepines are so commonly prescribed, physicians need to keep these interactions in mind and exercise caution when they are prescribed together to avert any severe or fatal reactions.

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