



Drug-Drug Interaction between Psychiatric Medications and Experimental Treatments for Coronavirus Disease-19: A Mini-Review

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Abstract

The pandemic of coronavirus disease (COVID)-2019 has been affected many people all around the world. Patients with mental disorders are not as safe as others; also, they might be more vulnerable in such situations. These patients take various medications, which can lead to numerous drug-drug interactions with experimental drugs uses against COVID-19. According to the potential critical interactions, we reviewed the reputable databases to find the interactions between main categories of psychiatric medications (e.g., antidepressants, anti-psychotics, sedative/hypnotics, and mood stabilizers) when used in concomitant with COVID-19 experimental agents (e.g., hydroxychloroquine, lopinavir/ritonavir, atazanavir, and chloroquine). We hope the list provided in this review helps the clinical care staff in treating patients with mental illness infected with severe acute respiratory syndrome coronavirus 2 during the COVID-19 pandemic.

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported from Wuhan, China, in December 2019 [1] and rapidly spread worldwide to become a pandemic on March 12, 2020 [2]. No specific drug has been approved for the treatment of COVID-19 yet. Infectious Diseases Society of America has suggested a few agents based on limited clinical trials such as hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) [3]. Atazanavir (ATV) also has been supported by other documents to have a potential benefit for COVID-19 [4], [5].

Mental disorders are listed among the most common causes of chronic diseases. The prevalence was estimated to be 22.1% in 2019 [6]. This group of patients is not as safe as others; also, they might be more vulnerable in such situations [7], [8] due to probable cognitive impairment, lack of awareness regarding transmission risks, and poor personal hygiene [9]. The presence of comorbidities, such as mental disorders

in patients with COVID-19, makes the treatment plan more challenging [10]. One of these challenges is drug-drug interaction.

Ritonavir applies a paradoxical inhibitory/induction effect on cytochromes P450 (CYP) family 3, subfamily A (CYP3A) isoenzyme and is a moderate inhibitor against CYP2D6 isoenzyme [11]. ATV is a substrate and inhibitor of CYP isoenzyme 3A and inhibits/induces P-glycoprotein [12]. Therefore, these two medications have many significant drug interactions that may affect the outcome of patients. HCQ and chloroquine (CQ) are highly potential to prolong QT interval and may elevate the adverse effects of drugs in this direction [13].

Thus, we aimed to evaluate the interactions between psychiatric medications (consist of antidepressants, anti-psychotics, sedative/hypnotics, and mood stabilizers) and highly used experimental COVID-19 treatments including HCQ, CQ, LPV/r, and ATV, to help the clinician decisions in choosing appropriate medications with lowest drug-drug

interactions according to the underlying disease of patients.

Materials and Methods

We studied four reputable databases of drug interactions including Lexi-Interact [14], Drug Interactions Checker [15], UpToDate [16], HIV drug interactions [17], as well as Stockley's Drug Interactions Pocket Companion and AIDS *info* guidelines for the use of antiretroviral agents in adults and adolescents with HIV [18] to find out the interactions between four categories of psychiatric medications and experimental COVID-19 medications. Additional references (e.g., original articles and FDA drug information) were also included as needed.

Results

Concise and rapid guidance for drug-drug interactions is presented in Table 1. In this table, the

green color illustrates no clinically significant interaction, the yellow color mentions the need for monitoring or treatment modification, the red color represents contraindication of combination, and the blue color is used to demonstrate controversy among recommendations of different databases. The detailed information about the mechanism of interaction, consequences, and management were reviewed in this section.

Antidepressants

Citalopram/escitalopram

Citalopram/escitalopram is metabolized through CYP2C19, CYP2D6, and CYP3A4 isoenzymes [16].

Citalopram/escitalopram – HCQ/CQ

Mechanism and consequence

Both selective serotonin reuptake inhibitors (SSRIs) and HCQ/CQ may lead to QT prolongation [14], [15], [19] and hypoglycemia [14]. Concomitant use of these medications enhances such side effects.

Table 1: Rapid drug interactions guidance

Psychiatric medications		Experimental agents for COVID-19				
Drug category	Drugs name	Hydroxychloroquine	Chloroquine	Lopinavir+Ritonavir	Atazanavir	
Antidepressants	Citalopram	1.1.1	1.1.1	1.1.2	1.1.2	
	Escitalopram	1.1.1	1.1.1	1.1.2	1.1.2	
	Fluoxetine	1.2.1	1.2.1	1.2.2	1.2.3	
	Fluvoxamine	1.3.1	1.3.1	1.3.2	1.3.3	
	Paroxetine	1.4.1	1.4.2	1.4.3	1.4.4	
	Sertraline	1.5.1	1.5.1	1.5.2	1.5.3	
	Venlafaxine	1.6.1	1.6.1	1.6.2	1.6.2	
	Duloxetine	1.7.1	1.7.1	1.7.2	1.7.2	
	Amitriptyline	1.8.1	1.8.1	1.8.2	1.8.2	
	Maprotiline	1.8.1	1.8.1	1.8.2	1.8.2	
	Nortriptyline	1.8.1	1.8.1	1.8.2	1.8.2	
	Desipramine	1.8.1	1.8.1	1.8.2	1.8.2	
	Doxepin	1.9.1	1.9.1	1.9.2	1.9.2	
	Clomipramine	1.10.1	1.10.1	1.10.2	1.10.2	
	Imipramine	1.10.1	1.10.1	1.10.2	1.10.2	
	Bupropion	1.11.1	1.11.2	1.11.3	1.11.4	
	Buspirone	1.12.1	1.12.1	1.12.2	1.12.2	
	Mirtazapine	1.13.1	1.13.1	1.13.2	1.13.2	
	Trazodone	1.13.1	1.13.1	1.13.2	1.13.2	
	Anti-psychotics	Aripiprazole	2.1.1	2.1.1	2.1.2	2.1.3
Clozapine		2.2.1	2.2.1	2.2.2	2.2.2	
Olanzapine		2.3.1	2.3.1	2.3.2	2.3.3	
Quetiapine		2.4.1	2.4.1	2.4.2	2.4.2	
Risperidone		2.5.1	2.5.1	2.5.2	2.5.3	
Chlorpromazine		2.6.1	2.6.1	2.6.2	2.6.3	
Fluphenazine		2.6.1	2.6.1	2.6.2	2.6.3	
Perphenazine		2.6.1	2.6.1	2.6.2	2.6.3	
Thioridazine		2.6.1	2.6.1	2.6.2	2.6.3	
Haloperidol		2.7.1	2.7.1	2.7.2	2.7.2	
Pimozide		2.8.1	2.8.1	2.8.2	2.8.2	
Sedative hypnotics		Alprazolam	3.1.1	3.1.1	3.1.2	3.1.3
		Chlordiazepoxide	3.1.1	3.1.1	3.1.2	3.1.3
		Clonazepam	3.1.1	3.1.1	3.1.2	3.1.3
	Diazepam	3.1.1	3.1.1	3.1.2	3.1.3	
	Temazepam	3.2	3.2	3.2	3.2	
	Lorazepam	3.2	3.2	3.2	3.2	
	Oxazepam	3.2	3.2	3.2	3.2	
	Triazolam	3.3.1	3.3.1	3.3.2	3.3.2	
	Midazolam	3.3.1	3.3.1	3.3.2	3.3.2	
	Zolpidem	3.4.1	3.4.1	3.4.2	3.4.2	
Mood stabilizers	Carbamazepine	4.1.1	4.1.2	4.1.3	4.1.4	
	Valproic acid	4.2.1	4.2.2	4.2.3	4.2.4	
	Lithium	4.3.1	4.3.1	4.3.1	4.3.2	
	Lamotrigine	4.4.1	4.4.2	4.4.3	4.4.4	

Red color: Extremely significant interaction. Contraindicated. Yellow color: Minimally or moderately significant interaction. Monitoring or therapy modification is needed. Blue color: Controversy between different references. Green color: No significant interaction or does not require any action. The paragraph number is cited in the table, Ctrl + Click on paragraph number to refer to the related section of the article for additional information.

Management

It is recommended to use caution in the elderly, females, individuals with a history of cardiovascular disease, hypokalemia, and hypomagnesemia. Close monitoring for QT prolongation and hypoglycemia is required [14], [15].

Citalopram/escitalopram – LPV/r and ATV

Mechanism and consequence

Coadministration of either LPV/r or ATV with citalopram/escitalopram is associated with increased serum concentrations of these medications and QT prolongation effects [17], [18], [19].

Management

It is recommended to initiate SSRIs with the lowest dose and titrate slowly. Regular electrocardiogram (ECG) monitoring and correcting electrolyte abnormalities (hypokalemia or hypomagnesemia) may be required, especially in patients with a previous history of cardiovascular disease or electrolyte abnormalities [15], [17], [18].

Fluoxetine

Fluoxetine is a significant substrate of CYP2C9 and CYP2D6 isoenzymes [16].

Fluoxetine – HCQ/CQ

The interactions are similar to those mentioned for citalopram/escitalopram (Refer to 1.1.1).

Fluoxetine – LPV/r

Mechanism and consequence

Inhibitory effect of LPV/r on the CYP2D6 isoenzyme is predicted to raise the serum concentration of fluoxetine. Furthermore, fluoxetine can increase ritonavir [15], [17], [19], [20]. Serotonin syndrome is reported in a case series of patients that used ritonavir-based HAART with fluoxetine [21]. On the other hand, decreased concentrations of fluoxetine were observed when combined with ritonavir-boosted protease inhibitors (PIs) [22].

Management

Careful monitoring of adverse effects and dose adjustment for fluoxetine may be needed [15], [17], [18], [22].

Fluoxetine – ATV

There are no clinically significant interactions [14], [15], [17], [22].

Fluvoxamine

Fluvoxamine is mainly metabolized through the CYP2D6 isoenzyme [16].

Fluvoxamine – HCQ/CQ

Mechanism and consequence

SSRIs may increase insulin sensitivity and enhance the hypoglycemic effects of HCQ/CQ [14]. Moreover, a study reports an increase in the concentrations of HCQ/CQ [19], while two others do not mention any significant interactions [15], [22].

Management

Monitor for the hypoglycemic effects of medications is required [14].

Fluvoxamine – LPV/r

Mechanism and consequence

Coadministration has not been studied. LPV/r could potentially increase fluvoxamine concentrations by the inhibitory effect of ritonavir on the CYP2D6 isoenzyme [17], [19].

Management

No dosage adjustment is recommended [17]. However, according to another reference, consideration of an alternative antidepressant may be needed [23].

Fluvoxamine – ATV

No clinically significant interactions were found [14], [15], [17], [19], [22].

Paroxetine

Paroxetine is a major substrate for CYP2D6 isoenzyme [16].

Paroxetine – HCQ

Interactions are similar to those of fluvoxamine (Refer to 1.3.1).

Paroxetine – CQ

Mechanism and consequence

Paroxetine concentrations may rise following inhibition of CYP2D6 isoenzyme [14], [19].

Management

Monitor for increased drug effects, and hypoglycemia is recommended [14].

Paroxetine – LPV/r

Mechanism and consequence

LPV/r can increase the serum concentration of paroxetine due to the inhibitory effect of ritonavir on the CYP2D6 isoenzyme [15], [17], [18], [22]. Moreover, decreased paroxetine concentrations are reported with ritonavir-boosted PIs [22].

Management

Monitoring of adverse effects and probably dose adjustment of paroxetine may be required [15], [17], [18], [22].

Paroxetine – ATV

Mechanism and consequence

Interactions are controversial among different studies. Some references mention that there is no significant interaction [14], [15], while some others point to the same interaction that exists for LPV/r (refer to 1.4.3) [17], [18].

Management

As mentioned for LPV/r (refer to 1.4.3) [17], [18].

Sertraline

Sertraline is a minor substrate for CYP2B6, CYP2C9, CP2C19, and CYP3A4 isoenzymes [16].

Sertraline – HCQ/CQ

Refer to citalopram/escitalopram (1.1.1) [14], [15].

Sertraline – LPV/r

Mechanism and consequence

LPV/r may decrease the sertraline concentration through induction of CYP2B6, CYP2C9, and CP2C19 isoenzymes [17], [19], [22].

Management

Monitoring for the efficacy of sertraline and dose titration may be required [17], [22].

Sertraline – ATV

Mechanism and consequence

Sertraline exposure may increase by inhibition of CYP3A4 isoenzyme [17], [19], [24].

Management

Dose adjustment may not be required [17].

Venlafaxine**Venlafaxine – HCQ/CQ**

Mechanism and consequence

Although some references did not report any interactions [14], [22], studies reported that both medications could prolong the QT interval [15], [19].

Management

Monitoring QT interval and correction of hypokalemia and hypomagnesemia may be necessary [15], [19].

Venlafaxine – LPV/r and ATV

Mechanism and Consequence

Venlafaxine concentration may be increased if either ATV or LPV/r is simultaneously administered through an inhibitory effect on the CYP3A4 isoenzyme [15], [17], [19], [24].

Management

Dose adjustment is not required, but it is recommended to use it with caution [15], [17], [24].

Duloxetine

Duloxetine is a major substrate of CYP1A2 and a minor substrate of CYP2D6 isoenzymes [16].

Duloxetine – HCQ/CQ

Mechanism and consequence

Plasma concentrations of duloxetine may be elevated through inhibitory effects on CYP2D6 isoenzyme [14], [15], [19].

Management

Monitor for adverse reactions and adjust the dose, if needed [14], [15].

Duloxetine – LPV/r and ATV

Ritonavir induces CYP1A2 and inhibits CYP2D6 isoenzymes; thus, the consequence of interaction is unpredictable, and dose adjustment may not be essential. ATV does not significantly affect duloxetine concentrations [15], [17], [19], [24].

Amitriptyline/nortriptyline/maprotiline/desipramine

These tricyclic antidepressants (TCAs) are major substrates of CYP2D6 isoenzyme [16].

Amitriptyline/Nortriptyline/Maprotiline/Desipramine – HCQ/CQ

Mechanism and consequence

Coadministration of two medications with QT prolongation effects causes additive adverse effects, including torsade de pointes arrhythmias [15].

Management

Correction of risk factors (e.g., hypokalemia and hypomagnesemia) and ECG monitoring may be required [15]. Some references mention that there is no need for taking action [14], [22].

Amitriptyline/Nortriptyline/Maprotiline/Desipramine – LPV/r and ATV

Mechanism and consequence

The serum concentration of the TCAs may be increased with the administration of LPV/r due to inhibitory effects on CYP2D6 isoenzyme [14], [18], [19], [22], [24]. However, it seems that unboosted ATV does not have this inhibitory effect, and enhanced TCA plasma concentrations are not expected [17].

Management

Monitor for adverse effects of TCAs, and dose reduction may be implemented in the case of coadministration with LPV/r. Furthermore, monitor for decreased effects of TCAs if the LPV/r is discontinued. EKG monitoring is also recommended for concomitant administration of LPV/r or ATV with mentioned TCAs, due to QT prolongation [14], [17], [18], [19].

Doxepin

Doxepin – HCQ/CQ

Use with caution is recommended due to QT prolongation, as mentioned in the 1.8.1 section [14], [15].

Doxepin – LPV/r and ATV

The mechanism and consequence of interaction are the same as other TCAs in 1.8.2 section. However, the management, in this case, is controversial; some studies recommended careful monitoring of adverse effects, and a decrease in the dose of doxepin may be required [14], [15], [18], [22], [24]. In contrast, others believe that no dose adjustment is needed [17], [19].

Imipramine/clomipramine

These TCAs are metabolized through CYP2D6, CYP2C19, and CYP1A2 isoenzymes [16].

Imipramine/Clomipramine – HCQ/CQ

Monitor for QT interval prolongation, as mentioned for other TCAs (section 1.8.1).

Imipramine/Clomipramine – LPV/r and ATV

Mechanism and consequence

Both LPV/r and ATV may increase the serum concentration of mentioned TCAs due to inhibitory effects on the CYP450 isoenzymes [14], [15], [17], [18], [19], [22], [24].

Management

Close monitoring of adverse effects, including QT prolongation, is recommended. Furthermore, a decrease in the dose of TCAs may be required [14], [15], [17], [18], [22].

Bupropion

Bupropion is a major substrate of CYP2B6 isoenzyme [16].

Bupropion – HCQ

No clinically significant interaction was reported [14], [15], [22].

Bupropion - CQ

Mechanism and consequence

Bupropion is a potent inhibitor of CYP2D6 isoenzyme and increases CQ exposure [14]. On the other hand, bupropion applies the dose-dependent risk of seizures, mostly when used concomitantly with medications that decrease the threshold of seizures (e.g., CQ) [15].

Management

Both medications should be initiated with lower doses and titrate slowly based on clinical response. If seizures occur during treatment with bupropion, the drug should be discontinued permanently [15].

Bupropion – LPV/r

Mechanism and consequence

LPV/r reduces the area under curve (AUC) of bupropion by 57% [14], [15], [17], [18], [19], [22], [24], [25]. It seems that the induction of CYP2B6 isoenzyme by ritonavir leads to this interaction, contrary to *in vitro* data, which reports inhibition of CYP2B6 by ritonavir [14], [26].

Management

The efficacy of bupropion treatment should be monitored. Initiating therapy with higher doses is not recommended, but titration of bupropion dose is suggested based on clinical response [14], [15], [17], [18], [22].

Bupropion – ATV

There is no clinically significant interaction [14], [15], [17], [18], [19], [22].

Buspirone

Buspirone is metabolized mainly through the CYP3A4 pathway [16].

Buspirone – HCQ/CQ

No significant interactions were found [14], [15], [22].

Buspirone – LPV/r and ATV

Mechanism and consequence

Inhibitors of CYP3A4 isoenzyme increase the plasma concentrations of buspirone and may lead to Parkinson-like symptoms [14], [15], [17], [18], [22].

Management

It is recommended to initiate therapy with the lowest dose of buspirone and titrate based on clinical response followed by monitoring adverse reactions [14], [15], [17], [18], [22].

Mirtazapine/trazodone**Mirtazapine/trazodone – HCQ/CQ**

There is no particular recommendation in this regard. Some references did not report a significant interaction [14], [22], but others have focused on the risk of QT prolongation and recommend using caution in susceptible patients [15], [19].

Mirtazapine/Trazodone – LPV/r and ATV

Mechanism and consequence

Either LPV/r or ATV can increase the serum concentrations of mirtazapine/trazodone [14], [15], [17], [19], [22], [24] through inhibition of CYP3A4 isoenzyme [14], [17].

Management

It is recommended to initiate therapy with lower doses and monitor increased central nervous system adverse effects and QT prolongation [14], [15], [17], [22].

Anti-psychotics**Aripiprazole**

Aripiprazole is mainly metabolized through CYP2D6 and CYP3A4 isoenzymes [16].

Aripiprazole – HCQ/CQ

Mechanism and consequence

The risk of clinically significant QT prolongation is not definite [15].

Management

No action is needed [14], [22]. According to some references, QT prolongation may occur in patients with underlying cardiovascular disease or concomitant use of medications, which cause QT prolongation [15], [19], and close ECG monitoring may be required [15].

Aripiprazole – LPV/r**Mechanism and consequence**

LPV is a potent inhibitor of CYP 3A4, and ritonavir is a strong inhibitor of CYP3A4 and CYP2D6 isoenzymes. Thus, increased plasma concentrations of aripiprazole are anticipated [14], [22], [24]. Besides, QT prolongation may occur, but it is uncertain [15], [19].

Management

Pharmacological responses should be monitored. Up to 75% dose reduction for aripiprazole may be needed [14], [18]. ECG monitoring is recommended based on some references [15], [19].

Aripiprazole – ATV**Mechanism and consequence**

ATV inhibits the CYP3A4 pathway and may increase the plasma concentration of aripiprazole [14], [15], [17], [24].

Management

Aripiprazole dose reduction may be required up to 50% [14], [15], [17], [18], [22]. Consider up to 75% dose reduction if concomitant CYP2D6 isoenzyme inhibitors are used [14].

Clozapine

Clozapine is a major substrate of CYP1A2 and a minor substrate of CYP3A4 and CYP2D6 isoenzymes.

Clozapine – HCQ/CQ**Mechanism and consequence**

Both clozapine and antimalarial medications have similar adverse effects such as QT interval prolongation and agranulocytosis, which may increase concomitant use of these medications [14], [15].

Management

Use with caution and monitor for adverse reactions. Discontinue treatment if the QT interval increased more than 500 milliseconds (ms). Modifiable risk factors (e.g., hypokalemia and hypomagnesemia) should be corrected [14], [15].

Clozapine – LPV/r and ATV**Mechanism and consequence**

Clozapine plasma concentrations may be increased [14], [15], [17], [18], [19], [22] through

inhibitory effects of LPV/r and ATV on hepatic isoenzymes [14], [17].

Management

Clozapine should be initiated with lower doses and titrate gradually with monitoring adverse reactions (e.g., QT prolongation) [14], [15], [17], [18], [24]. Some references suggest avoiding concomitant use of LPV/r with clozapine due to severe hematologic side effects [22].

Olanzapine

Olanzapine is a major substrate of CYP1A2 and a minor substrate of CYP2D6 isoenzyme [16].

Olanzapine – HCQ/CQ**Mechanism and consequence**

Some references mention that QT prolongation could occur in high-risk patients [14], [15].

Management

Close ECG monitoring and modifying risk factors may be helpful [14], [15]. One reference does not indicate this interaction [19].

Olanzapine – LPV/r**Mechanism and consequence**

Ritonavir induces CYP1A2 isoenzyme and leads to decreased (up to 50%) olanzapine concentrations [14], [15], [17], [19], [22], [23], [24], [27].

Management

Close monitoring for the efficacy of olanzapine and dose adjustment may be required [14], [15], [17], [22]. Furthermore, some references advise monitoring QT intervals in high-risk populations [15].

Olanzapine – ATV

There are no clinically significant interactions [14], [15], [17], [19], [22].

Quetiapine

Quetiapine is mainly metabolized through CYP3A4 hepatic isoenzyme [16].

Quetiawpine – HCQ/CQ

As mentioned for olanzapine – HCQ/CQ (Refer to 2.3.1) [14], [15], [19]. Furthermore, due to additive hypoglycemic effects of concomitant QC administration, one reference advices to monitor for hypoglycemia [14].

Quetiawpine – LPV/r and ATV

Mechanism and consequence

PIs increase the AUC of quetiawpine (up to 6 times) by inhibiting CYP3A4 isoenzyme.

Management

Some references recommend avoiding coadministration [17], [19]; however, some recommend using lower doses of quetiawpine. Initiate with the lowest dose of quetiawpine and titrate gradually based on the adverse effects and efficacy of the medication. If the patient is stable on a specific dose of quetiawpine, it is recommended to reduce the dose by 1/6, if PI is required. Monitor for adverse effects, including QT prolongation [14], [15], [18], [22], [23], [24].

Risperidone

Risperidone is a major substrate of CYP2D6 and CYP3A4 isoenzymes and P-glycoprotein/ABCB1.

Risperidone – HCQ/CQ

The same as olanzapine (Refer to 2.3.1) [14], [15], [19], [22].

Risperidone – LPV/r

Mechanism and consequence

LPV/r increases risperidone exposure through inhibitory effects on CYP2D6 isoenzyme and P-glycoprotein/ABCB1 [14], [15], [17], [19], which may cause risperidone dependent adverse effects including extrapyramidal syndrome and neuroleptic malignant syndrome [17], [22]. Furthermore, dose-dependent QT interval prolongation may occur [14], [15], [17], [22].

Management

Decreased risperidone dose and monitoring for adverse drug reactions are required [14], [15], [17], [18], [22].

Risperidone – ATV

Some references indicate the same interactions that mentioned about LPV/r (refer

to 2.5.2) [17], [18], [19], but others declare no interactions between risperidone and ATV [14], [15], [22].

Chlorpromazine/fluphenazine/perphenazine/thioridazine

These medications are metabolized mainly through CYP2D6 isoenzyme [16].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – HCQ/CQ

Mechanism and Consequence

In addition to the QT prolongation effect, which was mentioned for other anti-psychotics, anti-malaria agents could increase the concentrations of phenothiazine-based anti-psychotics by an unknown mechanism [14], [19].

Management

Monitoring for side effects (e.g., QT prolongation) and modifying underlying risk factors should be considered [14], [15], [19].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – LPV/r

Mechanism and consequence

LPV/r could potentially increase plasma concentrations of these anti-psychotics. Additive QT interval prolongation may occur in coadministration [14], [15], [17], [19].

Management

Use with caution as stated for CQ and HCQ (refer to 0) [14], [15], [17], [19].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – ATV

There are inconclusive data. Some references report no interactions [14], [15]; however, one reference remarks QT prolongation in coadministration and recommends close monitoring in this regard [17].

Haloperidol

Haloperidol has a complex pathway of metabolism, including glucuronidation, oxidation, CYP3A4, and CYP2D6 isoenzymes mediated reactions [16], [17].

Haloperidol – HCQ/CQ**Mechanism and Consequence**

Concomitant administration of two medications with QT interval prolongation may have additive side effects and lead to serious cardiac arrhythmias. This interaction is more frequent when higher doses or intravenous haloperidol is administered [14], [15], [19].

Management

Close monitoring for adverse reactions and correcting modifiable risk factors such as electrolyte abnormalities are necessary [14], [15].

Haloperidol – LPV/r and ATV**Mechanism and consequence**

LPV/r and ATV increase haloperidol exposure by inhibition of CYP2D6 and CYP3A4 isoenzymes, which may lead to increased adverse effects such as QT prolongation [14], [15], [17], [24].

Management

Use caution and monitor as mentioned for HCQ and CQ (Refer to 2.7.1) [14], [15], [17].

Pimozide

Pimozide is metabolized through CYP3A4 isoenzyme.

Pimozide – HCQ/ CQ**Mechanism and Consequence**

QT interval prolongation is the main interaction, as mentioned for concomitant use of other anti-psychotics with other medications that have the same effect [14], [15], [19].

Management

Most of the references advise to avoid coadministration of CQ [14], [15], but there are controversial recommendations regarding HCQ. One database recommends avoidance [15]; however, another one suggests not taking any action [14], and the other reference advises monitoring for adverse effects [19].

Pimozide – LPV/r and ATV

Concomitant use of pimozide with PIs is contraindicated due to increased pimozide levels by

CYP3A4 isoenzyme inhibitory effects of PIs. Increased exposure to pimozide may lead to lethal cardiac arrhythmias [14], [15], [17], [18], [19], [22], [24].

Sedative/Hypnotics**Alprazolam/chlordiazepoxide/clonazepam/diazepam**

These medications are major substrates of CYP 3A4 isoenzyme [16].

Alprazolam/Chlordiazepoxide/Clonazepam/Diazepam – HCQ/CQ

There are no clinically significant interactions [14], [15], [19], [22].

Alprazolam/Chlordiazepoxide/Clonazepam/Diazepam – LPV/r**Mechanism and Consequence**

LPV/r may increase the plasma concentrations of mentioned benzodiazepines by inhibiting the CYP3A4 pathway [14], [15], [17], [28].

Management

Monitor for increased adverse reactions of benzodiazepines and reduce medication dose if needed, especially in the initiation of therapy. It is recommended to use alternative benzodiazepines with less probable interactions such as lorazepam, oxazepam, and temazepam [14], [15], [17], [18], [23]. There are conflicting data regarding the coadministration of diazepam and ritonavir. Some references recommended avoiding this combination, but most of them recommended monitoring, dose adjustment, or using alternative medications when ritonavir is used as a booster (e.g., LPV/r) [17], [22], [23].

Alprazolam/Chlordiazepoxide/Clonazepam/Diazepam – ATV**Mechanism and consequence**

ATV may increase the serum concentrations of these benzodiazepines, but there is no ample clinical evidence [14], [17], [18], [19].

Management

As stated for LPV/r [14], [17], [18].

Temazepam/lorazepam/oxazepam

These medications are metabolized through non-CYP450 hepatic pathways [16]; thus, there are no clinically significant interactions with HCQ, CQ, LPV/r, and ATV [14], [15], [16], [17], [18], [19].

Triazolam/midazolam*Triazolam/midazolam – HCQ/CQ*

No clinically significant interaction was reported [14], [15], [19], [22].

Triazolam/Midazolam – LPV/r and ATV

Mechanism and consequence

LPV/r inhibits CYP3A4 isoenzyme; therefore, the concentrations of mentioned benzodiazepines are increased, which may lead to respiratory failure [14], [15], [17], [18], [19], [23], [29].

Management

The administration of triazolam/oral midazolam should be avoided. The parental form of midazolam could be used with caution and reduced dose [14], [15], [17], [18], [19].

Zolpidem/zopiclone

These medications are mainly metabolized through CYP3A4 isoenzyme [16].

Zolpidem/Zopiclone – HCQ/CQ

No clinically significant interaction was reported [14], [15], [19], [22].

Zolpidem/Zopiclone – LPV/r and ATV

Mechanism and consequence

Increased sedation may occur due to inhibition of CYP3A4 isoenzyme.

Management

Patients should be monitored closely. Reducing the dose of zolpidem/zopiclone may be required [14], [15], [17], [18], [19], [29].

Mood stabilizers**Carbamazepine**

Carbamazepine is a strong CYP3A4 isoenzyme inducer [16]. *Carbamazepine – HCQ*

No clinically significant interaction was found [14], [15]; however, according to one reference, this combination should be avoided [19].

Carbamazepine – CQ

Mechanism and consequence

Carbamazepine may decrease the plasma concentration of CQ through CYP3A4 pathway induction [14], [15]. CQ-induced seizures have been reported [15], [16].

Management

Monitor for decreased effects of CQ [14] and use with caution in patients with a history of seizure [15], [16]. One reference recommended avoiding combination [19].

Carbamazepine – LPV/r

Mechanism and consequence

Carbamazepine may decrease the LPV/r concentrations, and LPV/r may increase the carbamazepine concentrations in plasma through the CYP3A4 pathway [14], [24], [30], [31].

Management

Consider alternative medications and monitor plasma concentrations of carbamazepine [14], [17]. An increment in LPV/r may be required [17]. Once-daily administration of LPV/r should be avoided [17], [18], [24].

Carbamazepine – ATV

Mechanism and consequence

Decreased plasma concentrations of ATV due to the induction of CYP3A4 isoenzyme, which may lead to viral resistance [14], [15], [17]. Carbamazepine concentrations may be increased through CYP3A4 isoenzyme inhibition [14], [17].

Management

Coadministration should be avoided [15], [17], [18]; if the use of combination is necessary, plasma concentrations of carbamazepine should be monitored [17].

Valproate*Valproate – HCQ*

There is no clinically significant interaction [14], [15], [19].

Valproate – CQ**Mechanism and consequence**

Seizure threshold may be decreased by CQ [15]. According to some other references, no clinically significant interaction was found [14], [19], [22].

Management

Use CQ with caution in patients with seizures [15].

Valproate – LPV/r**Mechanism and consequence**

The combination increases the AUC of LPV by up to 38%. Valproate serum concentrations are decreased through induction of CYP450 enzymes, especially glucuronosyltransferases [15], [17], [18], [22], [24], [32], [33].

Management

Monitor clinical response and serum levels of valproate [14], [17], [18], [22].

Valproate – ATV**Mechanism and consequence**

ATV may decrease serum levels of valproate [14], [18]. Some other studies did not report this interaction [17], [19], [22].

Management

Clinical response and serum concentrations of valproate should be monitored [14], [18].

Lithium**Lithium – HCQ/CQ/LPV/r****Mechanism and consequence**

Lithium and CQ/HCQ/LPV/r can prolong QT interval, especially in patients with underlying cardiovascular disease or electrolyte abnormalities [15], [19].

Management

Correction of electrolyte abnormalities and monitoring symptoms of QT prolongation is required [15].

Lithium – ATV

No clinically significant interaction was found [14], [15], [19], [22].

Lamotrigine**Lamotrigine – HCQ**

There is no clinically significant interaction [14], [15], [19], [22].

Lamotrigine – CQ**Mechanism and consequence**

CQ-induced seizure may occur [15], [16]. Other references indicated no significant interaction [14], [19], [22].

Management

Use CQ with caution in patients with a history of seizures [15], [16].

Lamotrigine – LPV/r**Mechanism and consequence**

The glucuronidation of lamotrigine enhances by LPV/r [14], [15]; thus, the lamotrigine AUC and half-life reduce by 50% [14], [17], [18], [24], [34].

Management

The lamotrigine dose increment may be needed [17], [18], [22].

Lamotrigine – ATV**Mechanism and consequence**

ATV may decrease the lamotrigine AUC up to 12%, but it is not clinically significant [22], [35].

Management

Monitor serum levels of lamotrigine. Approximately all references recommended no need for dose adjustment [14], [15], [17], [18], [19], [22].

Discussion

Physicians, psychologists, pharmacologists, pharmacotherapists, and other drug experts are

at the forefront during the COVID-19 pandemic. Pharmacological consultants were always needed hospital care procedures [36]. Furthermore, to provide an up to date information for public and specialists population, application of pharmacokinetic and pharmacodynamic investigations, especially during clinical trials, is essential [37], [38]. In this regard, the study of drug interactions is an important pharmacological preventive procedure to manage multiple drug consumption consequences. Hence, assessing drug-drug interactions with particular focus on psychiatric medications during the COVID-19 pandemic is highly vital, while many patients in different age categories suffer from mental disorders, and their conditions have worsened due to the current situation, especially during quarantine and isolation.

More than 300 clinical trials on various therapeutic approaches are ongoing for COVID-19 [15]. Some of the tested medications, in this case, are highly potential for interacting with individuals' chronic treatments. These interactions mostly appear due to pharmacokinetic features such as induction/inhibitory effects on cytochrome isoenzymes and renal excretion, or pharmacodynamic properties such as QT prolongation. Furthermore, due to the extensive inflammation in COVID-19 patients, the pharmacokinetic performance of the drugs can be affected through organ dysfunction, CYP isoenzymes downregulation, plasma proteins modification, etc. [39], [40], [41].

Hence, psychiatric drug interactions with experimental agents administered for COVID-19 should be considered carefully. Interactions between psychotropic drugs and drugs used for the treatment of COVID-19 have a wide range of severity from slight changes in the plasma level of the affected drug to life-threatening conditions [42]. Thus, it was essential to prepare a detailed list of all widely used medications in such patients to improve outcomes and prevent adverse drug reactions and drug-drug interactions. We hope the list provided in this review helps the clinical care staff in treating such patients during the COVID-19 pandemic.

Conclusion

Knowledge about SARS-CoV-2 infection is still evolving. There are various projected medications for COVID-19 patients, which might be used in individuals under other chronic treatments, especially patients with mental disorders. Concomitant consumption of these medications may lead to drug interactions and acute adverse effects on the patient's outcome. However, the risk of such interactions can be manageable through an ample knowledge of pharmacokinetic and pharmacodynamic regarding these drugs. Eventually, safe treatment in these patients could be managed by applying measures such as close monitoring,

dosage adjustment, and considering relative/absolute contraindications and indications.

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