REVIEW ARTICLE

Clinically Significant Drug Interactions Between Psychotropic Agents and Repurposed COVID-19 Therapies

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Abstract

As many patients with underlying psychiatric disorders may be infected with COVID-19, and COVID-19-affected subjects may frequently experience a new onset of psychiatric manifestations, concomitant use of psychotropic medications and COVID-19 therapies is expected to be highly likely and raises concerns of clinically relevant drug interactions. In this setting, four major mechanisms responsible for drug interactions involving psychotropic agents and COVID-19 therapies may be identified: (1) pharmacokinetic drug–drug interactions mainly acting on cytochrome P450; (2) pharmacodynamic drug–drug interactions resulting in additive or synergistic toxicity; (3) drug–disease interactions according to stage and severity of the disease; and (4) pharmacogenetic issues associated with polymorphisms of cytochrome P450 isoenzymes. In this review, we summarise the available literature on relevant drug interactions between psychotropic agents and COVID-19 therapies, providing practical clinical recommendations and potential management strategies according to severity of illness and clinical scenario.

1 Introduction

The coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2, first identified in the Wuhan State of China at the end of 2019 [1]. COVID-19 was stated as a public health emergency of international concern on 30 January, 2020, and subsequently listed as a global pandemic on 11 March, 2020 by the World Health Organization [2, 3]. As of 13 March, 2021, more than 117 million cases and 2.5 million deaths were reported in 220 countries [4]. COVID-19 may be responsible for variable clinical manifestations, from an asymptomatic infection to severe respiratory distress syndrome associated with multi-organ failure [5].

Currently, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have recommended granting a marketing authorisation only to remdesivir [6, 7]. Specifically, remdesivir is approved only for adults and adolescents (aged ≥ 12 years) with COVID-19

Key Points

Clinically relevant drug interactions between psychotropic agents and COVID-19 agents may result from pharmacokinetic/pharmacodynamic properties of the involved medications or may be caused by a drug–disease impact of moderate-to-severe forms of COVID-19, leading to multi-organ failure and a cytokine storm.

Lopinavir/ritonavir and darunavir/cobicistat pose the major concern in terms of clinically relevant interactions with psychotropic agents. Concomitant administration of protease inhibitors with haloperidol, quetiapine, ziprasidone, carbamazepine, midazolam and triazolam should be avoided because of increased toxicity. A low risk of clinically relevant interactions is expected with other COVID-19 agents (corticosteroids, heparin, immunomodulators, anti-JAK and remdesivir).

Psychotropic agents exhibiting a favourable pharmacokinetic/pharmacodynamic profile (sertraline, vortioxetine, milnacipran, olanzapine, paliperidone, oxazepam-like benzodiazepines) should be preferred in patients with COVID-19 requiring protease inhibitors.

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pneumonia requiring supplemental oxygen. Furthermore, the FDA recently granted an Emergency Use Authorization to the investigational neutralising IgG1 monoclonal antibodies bamlanivimab and casirivimab/imdevimab for treating recently diagnosed, mild-to-moderate COVID-19 infection in patients who are aged ≥ 12 years [8, 9]. However, off-label use of different agents (e.g. darunavir/cobicistat, lopinavir/ritonavir, tocilizumab, siltuximab, ruxolitinib, canakinumab, heparin, corticosteroids, colchicine) is currently implemented in patients with COVID-19, although several concerns in terms of efficacy and safety have been raised, including the risk of clinically relevant interactions with different classes of drugs [10–13].

Considering that many patients with underlying psychiatric disorders may be infected with COVID-19, and that up to 25% of patients affected by COVID-19 were shown to experience a new onset of psychiatric manifestations (such as anxiety, depression, insomnia, obsessive-compulsive disorder, reactive psychosis or post-traumatic stress disorder) [14–19], concomitant use of psychotropic medications and COVID-19 therapies is highly probable. Additionally, intensive care support and COVID-19 therapies showing psychiatric side effects might be an additional risk factor for the onset of psychiatric symptoms and delirium, requiring adequate treatment with psychotropic agents [20]. Psychotropic medications may be especially involved in clinically relevant drug interactions in the COVID-19 scenario, by virtue of: (1) extensive activity as substrates and/or inhibitors/inducers of cytochrome P450 (CYP) isoenzymes, thus potentially causing bidirectional pharmacokinetic (PK) interactions with COVID-19 therapies; (2) synergistic toxicity with different COVID-19 agents, leading to clinically relevant pharmacodynamic (PD) interactions (e.g. QT prolongation); (3) the relevant impact of COVID-19 in causing multiple organ failure (e.g. liver and renal impairment, haematological effects), and a cytokine storm relevantly affecting both PK/PD properties of psychotropic medications and CYP activity, thus resulting in significant drug–disease interactions [20–24]. Cytokine release syndrome represents a life-threatening systemic inflammatory syndrome involving elevated levels of circulating cytokines and immune-cell hyperactivation, and may play a major role in causing multi-organ failure in the late stages of COVID-19 [24]. The elevated levels of circulating cytokines are responsible for both the impaired activity of different CYP450 isozymes and the use of several anti-inflammatory and/or immunomodulatory agents in severe forms of COVID-19, thus contributing to the occurrence of drug–drug and drug–disease interactions.

Notably, a close relationship between the severity of COVID-19, clinical scenarios (from outpatient to intensive care unit [ICU] admission), and the use of specific psychotropic and COVID-19 therapies may be identified (Fig. 1). Antiviral agents are considered more appropriate in the early phase of infection, characterised by viral replication, while immunomodulatory agents should be reserved for later stages, characterised mainly by systemic hyperinflammation [5]. Likewise, while long-term psychiatric therapies are usually maintained in outpatient/inpatient settings in cases of mild-to-moderate COVID-19 infection, these medications are commonly discontinued in cases of severe COVID-19 forms requiring ICU admission [25]. In these latter cases, psychotropic use is limited to a few agents for sedation and treatment of delirium. Consequently, clinically relevant interactions between psychotropic agents and COVID-19 therapies, although demonstrated in healthy volunteers or predicted according to PK/PD properties, may not occur considering that the two agents are not concomitantly used in a specific scenario.

Although different reviews concerning drug interactions between psychotropic medications and COVID-19 therapies have just been published [20–22], data focusing on clinically relevant interactions in different COVID-19 scenarios are limited. This review aims to summarise the available literature on relevant drug interactions between psychotropic agents and COVID-19 therapies, providing practical clinical recommendations and potential management strategies according to severity of illness and clinical scenario.

2 Search Strategy

A literature search was conducted on PubMed-MEDLINE (until 7 January, 2021) to retrieve PK and PD features of currently used COVID-19 therapies and psychotropic agents, specifically involved in the occurrence of relevant drug–drug interactions (DDIs) and drug–disease interactions, namely: (1) activity on CYP and other transporters (e.g. P-glycoprotein [P-gp]); (2) QT prolongation; and (3) significant variations affecting PK/PD properties of selected agents according to the severity of COVID-19 (e.g. organ failure, cytokine storm). Only studies conducted in humans and published in English were included.

Data concerning the activity on CYP450 and on transporters of psychotropic medications and COVID-19 agents were retrieved from the summary of product characteristics and the review of Smolders et al. [26]. Information on drug-induced QT prolongation were extracted from Crediblemeds.org [27]. QT drugs were classified respectively as agents with known risk (substantial evidence supports the conclusion that these drugs prolong QT intervals and have a risk of torsades de pointes when used as directed in labelling), possible risk (substantial evidence supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used
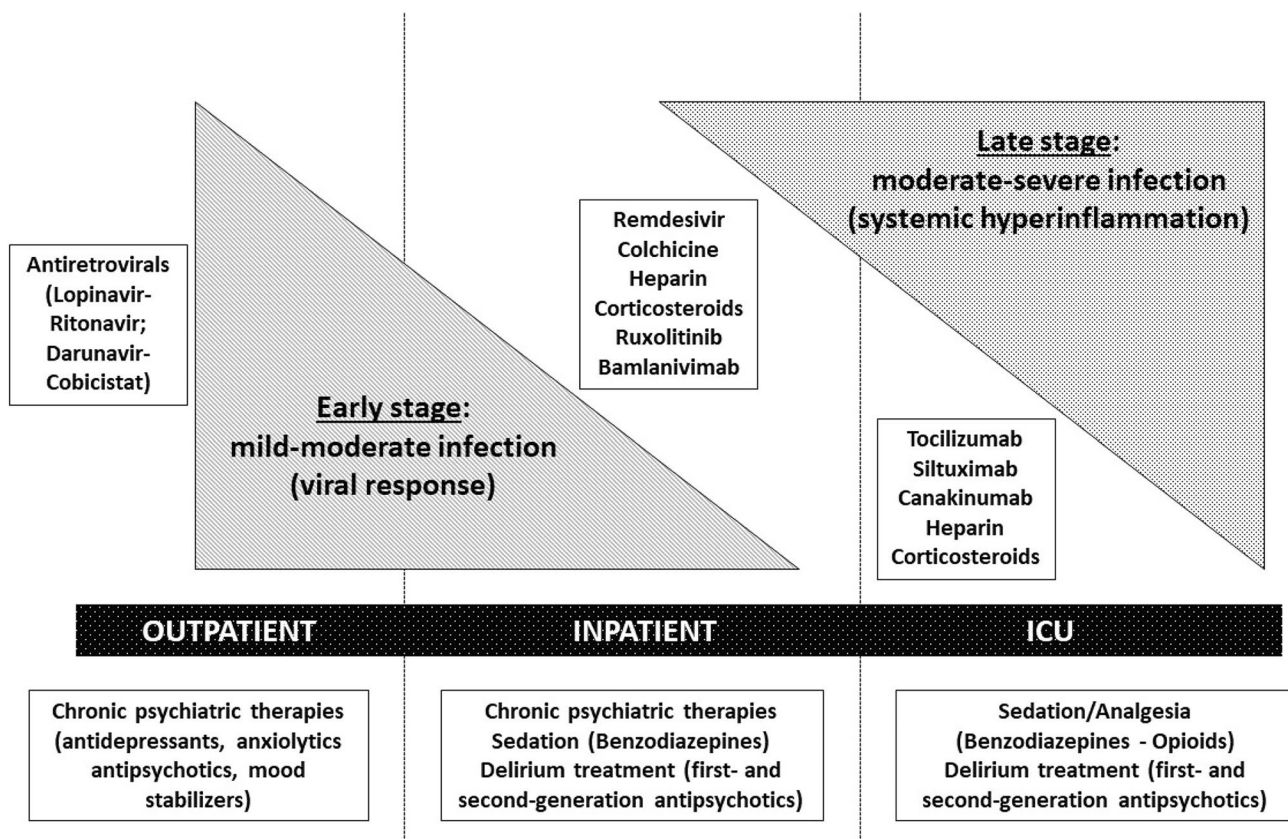
Fig. 1 Relationship between severity of COVID-19 disease, clinical scenarios, and use of specific psychotropic and COVID-19 therapies. *ICU* intensive care unit

as directed in labelling, have a risk of causing torsades de pointes) or conditional risk (substantial evidence supports the conclusion that these drugs prolong QT and have a risk of developing torsades de pointes but only under certain known conditions) [27].

Agents with a well-established use or under investigation for COVID-19 treatment were included in the analysis, namely: bamlanivimab, canakinumab, casirivimab/ imdevimab, colchicine, darunavir/cobicistat, dexamethasone, enoxaparin, lopinavir/ritonavir, remdesivir, ruxolitinib, siltuximab, tocilizumab. The following classes of psychotropic medications were investigated: antidepressants (agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, mianserin, milnacipran, mirtazapine, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, tranylcypromine, trazodone, venlafaxine, vortioxetine), antipsychotic agents (amisulpiride, aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, thioridazine, ziprasidone, zuclopenthixol), mood stabilisers (carbamazepine, lamotrigine, lithium, valproic

acid) and sedative hypnotics (alprazolam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, lormetazepam, midazolam, oxazepam, temazepam, triazolam, zolpidem, zopiclone).

A two-step approach was performed to detect clinically relevant drug interactions between psychotropic medications and COVID-19 agents. First, terms identifying psychotropic medications were combined with terms identifying COVID-19 therapies, to retrieve PK studies or case reports/series assessing the clinical relevance of the interaction according to the guideline provided by the EMA [28]. All studies or case series/reports providing PK data or describing clinically relevant PD events resulting from the coadministration of the two specific agents were included in our review. Second, information on drug–drug PK and PD interactions between psychotropic medications and COVID-19 agents was searched by checking the updated COVID-19 drug interaction webpage of the University of Liverpool [29] and the summaries of product characteristics. Drug–drug interactions were classified into three different categories according to the degree of severity and clinical relevance: (1) low risk, identifying agents exhibiting no predicted interaction;

(2) <u>moderate risk</u>, identifying agents exhibiting a predicted interaction according to PK/PD properties with unknown clinical relevance; (3) <u>high risk</u>, identifying agents exhibiting a clinically relevant interaction, for which avoidance of concomitant administration or dose adjustment should be considered. Finally, applicability in different COVID-19 scenarios was provided for each identified drug interaction, according to the severity of disease.

3 Major Mechanisms Responsible for Drug Interactions Involving Psychotropic Medications in the COVID-19 Era

Four major mechanisms responsible for drug interactions involving psychotropic agents and COVID-19 therapies may be identified: (1) PK interactions resulting in significant changes in disposition of psychotropic drugs or COVID-19 agents; (2) PD interactions resulting in additive or synergistic toxicity; (3) drug–disease interactions related to multi-organ failure and a cytokine storm commonly reported in moderate-to-severe COVID-19; and (4) pharmacogenetic issues associated with polymorphisms in CYP isoenzymes involved in the metabolism of both psychotropic and COVID-19 agents [20–24].

3.1 PK Interactions

Although drug interactions between psychotropic medications and COVID-19 therapies may theoretically involve each of the four PK ADME (absorption, distribution, metabolism, and elimination) phases [30], the most relevant mechanisms concern metabolic activity on the CYP microsomal system and drug transporters (mainly P-gp) according to lipophilic properties of psychotropic agents [26, 31, 32]. The influences of psychotropic medications and of COVID-19 therapies on CYP450 and drug transporters activities are summarised in Tables 1 and 2, respectively. Psychotropic agents are largely metabolised by the CYP system. The CYP2D6 and CYP2C19 isozymes are mainly involved in the metabolism of several antidepressants (including selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]) and antipsychotic medications (of both first and second generation), while different sedative hypnotics and mood stabilisers (apart from oxazepam-like benzodiazepines, valproic acid, lamotrigine and lithium) are metabolised by the CYP3A4 isozyme [26]. Additionally, concerns in terms of relevant drug interactions may arise as a result of inhibitory or induced activity on CYP. Fluoxetine, paroxetine and bupropion are strong inhibitors of CYP2D6, fluvoxamine is a strong inhibitor of both CYP1A2 and CYP2C19, whereas carbamazepine is a strong inducer of both CYP3A4 and P-gp [26]. With regard to COVID-19

therapies, the major issues in terms of relevant drug interactions may be associated with the use of antiretrovirals. Both darunavir/cobicistat and lopinavir/ritonavir are strong inhibitors of both CYP3A4 and CYP2D6. Colchicine and ruxolitinib are largely metabolised by CYP3A4, and thus their metabolism may be significantly affected in the case of coadministration with psychotropic medications that act as inhibitors or inducers of this isoenzyme.

3.2 PD Interactions

Clinicians should be aware that PD interactions may result in clinically relevant outcomes, triggered by additive or synergistic toxicity when certain psychotropic medications and COVID-19 therapies are concomitantly administered [10]. In this regard, several antidepressants and antipsychotic agents exhibit a well-established risk of QT prolongation (Table 1). The concomitant use of lopinavir/ritonavir may increase this risk by virtue of the PK/PD properties of this antiviral combination (Table 2), potentially leading to fatal arrhythmias [33]. Expected toxicity is commonly additive, extremely rarely synergistic. In the COVID-19 scenario, the main concerns involving PD interactions may be represented by the risk of QT prolongation and possible consequent fatal arrhythmias, coupled with additive haematological toxicity in patients co-treated with clozapine and ruxolitinib and/or anti-interleukin (IL)-1/6 agents.

3.3 Drug–Disease Interactions

The degree of severity of COVID-19 infection may be responsible for significant variations in the disposition of several psychotropic agents due to multi-organ failure and a cytokine storm commonly reported in moderate-to-severe forms of COVID-19 [34]. Specifically, the increased level of pro-inflammatory cytokines (e.g. IL-1 and IL-6) may consistently reduce the activity of CYP3A4, CYP1A2 and CYP2C19 [23, 35–37], and this may potentially affect the metabolism of those psychotropic agents that are substrates of these isoenzymes. Interestingly, among patients with severe COVID-19 treated with darunavir, a CYP3A4 substrate, it was shown that high IL-6 levels significantly decrease drug clearance [38]. This supports the idea that in severe forms of COVID-19, dosing optimisation of CYP3A4 substrates, including several psychotropic medications, may be needed. Conversely, no significant influence of pro-inflammatory cytokine levels was documented on CYP2D6 activity [23, 37]. This suggests that the metabolism of several antidepressants and antipsychotic agents that are CYP2D6 substrates should not be affected by the hyperimmune response observed in severe forms of COVID-19.

A cytokine storm usually occurs in patients with severe COVID-19 who may often need ICU admission [24]. In this

Table 1 Summary of the activity of the different psychotropic agents on CYP450. Activity on transporters and relevant PD effects (including QT prolongation) are also indicated

Agents	CYP1A2	CYP2C8/9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation
Antidepressants							
SSRIs							
Citalopram	Inhibitor (weak)	–	Substrate Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate	–	Known risk
Escitalopram	–	–	Substrate	Inhibitor (weak)	Substrate	–	Known risk
Fluoxetine	Substrate (minor) Inhibitor (weak)	Substrate Inhibitor (weak)	Substrate (minor) Inhibitor (moderate)	Substrate Inhibitor (strong)	Substrate (minor)	–	Conditional risk
Fluvoxamine	Substrate Inhibitor (strong)	Inhibitor (weak)	Inhibitor (strong)	Substrate Inhibitor (weak)	Inhibitor (weak)	–	Conditional risk
Paroxetine	Inhibitor (weak)	Inhibitor (weak)	Inhibitor (weak)	Substrate Inhibitor (strong)	–	–	Conditional risk
Sertraline	Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate (minor) Inhibitor (moderate)	Substrate (minor) Inhibitor (moderate)	Substrate (minor)	–	Conditional risk
Vortioxetine	–	Substrate (minor)	Substrate (minor)	Substrate	Substrate	P-gp: Substrate (minor) Inhibitor (weak)	–
SNRIs							
Desvenlafaxine	–	–	–	–	Substrate (minor)	UGT substrate	–
Duloxetine	Substrate	–	–	Substrate Inhibitor (moderate)	–	–	–
Reboxetine	–	–	–	Inhibitor (weak)	Substrate Inhibitor (weak)	–	–
Venlafaxine	–	Substrate (minor)	Substrate (minor)	Substrate Inhibitor (weak)	Substrate Inhibitor (weak)	–	Possible risk
TCAs							
Amitriptyline	Substrate (minor) Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate Inhibitor (weak)	Substrate (minor)	Substrate (P-gp)	Conditional risk
Clomipramine	Substrate	–	Substrate	Substrate Inhibitor (moderate)	Substrate (minor)	–	Conditional risk
Doxepin	Substrate (minor)	–	Substrate (minor)	Substrate	Substrate (minor)	–	Conditional risk
Imipramine	Substrate (minor) Inhibitor (weak)	–	Substrate Inhibitor (weak)	Substrate Inhibitor (moderate)	Substrate (minor)	–	Possible risk
Nortriptyline	Substrate (minor)	–	Substrate (minor)	Substrate Inhibitor (weak)	Substrate (minor)	Substrate (P-gp)	Possible risk
MAO-I							
Phenelzine	–	–	–	–	–	–	–
Tranylcypromine	–	–	–	–	–	–	–
Others							
Agomelatine	Substrate	Substrate	Substrate	–	–	–	–

Table 1 (continued)

Agents	CYP1A2	CYP2C8/9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation
Bupropion	Substrate (minor)	Substrate (minor)	–	Substrate (minor) Inhibitor (strong)	Substrate (minor)	Inhibitor (OCT2)	–
Mianserin	–	–	–	Substrate	–	–	Possible risk
Milnacipran	–	–	–	–	–	UGT substrate	–
Mirtazapine	Substrate Inhibitor (weak)	Substrate (minor)	–	Substrate	Substrate	–	Possible risk
Trazodone	–	–	–	Substrate (minor)	Substrate	Inducer (P-gp)	Conditional risk
Antipsychotic agents							
First-generation							
Amisulpiride	–	–	–	–	–	–	Conditional risk
Chlorproma-zine	Substrate (minor)	–	–	Substrate	Substrate (minor)	–	Known risk
Fluphenazine	Substrate Inhibitor (weak)	Inhibitor (weak)	–	Substrate Inhibitor (weak)	–	–	–
Haloperidol	Substrate (minor)	–	–	Substrate Inhibitor (moderate)	Substrate	–	Known risk
Perphenazine	Substrate (minor) Inhibitor (weak)	Substrate (minor)	Substrate (minor)	Substrate Inhibitor (weak)	Substrate (minor)	–	Possible risk
Pimozide	Substrate	–	Inhibitor (weak)	Substrate Inhibitor (weak)	Substrate	–	Known risk
Sulpiride	–	–	–	–	–	–	Known risk
Thioridazine	–	–	–	Substrate	Substrate (minor) Inducer (moderate)	–	Known risk
Second-generation							
Aripiprazole	–	–	–	Substrate	Substrate	–	Possible risk
Cariprazine	–	–	–	Substrate (minor)	Substrate	–	–
Clozapine	Substrate Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Substrate (minor) Inhibitor (moderate)	Substrate (minor) Inhibitor (weak)	–	Possible risk
Iloperidone	–	–	–	Substrate	Substrate	–	Possible risk
Lurasidone	–	–	–	–	Substrate Inhibitor (weak)	Substrate (P-gp)	Possible risk
Olanzapine	Substrate Inhibitor (weak)	Inhibitor (weak)	Inhibitor (weak)	Substrate (minor) Inhibitor (weak)	Inhibitor (weak)	UGT substrate	Conditional risk
Paliperidone	–	–	–	–	-	Inhibitor (weak; P-gp)	Possible risk
Quetiapine	–	–	–	Substrate (minor)	Substrate	–	Conditional risk
Risperidone	–	–	–	Substrate Inhibitor (weak)	Substrate (minor)	Substrate (P-gp)	Conditional risk
Sertindole	–	–	–	Substrate	Substrate	–	Known risk
Ziprasidone	–	–	–	–	Substrate (minor)	–	Conditional risk

Table 1 (continued)

Agents	CYP1A2	CYP2C8/9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation
Zuclopenthixol	–	–	–	Substrate	Substrate (minor)	–	Possible risk
Mood stabilisers							
Carbamazepine	–	Substrate (minor)	–	–	Substrate Inducer (strong)	Substrate (P-gp) Inducer (strong; P-gp)	–
Lamotrigine	–	–	–	–	–	UGT substrate	–
Lithium	–	–	–	–	–	–	Possible risk
Valproic acid	–	–	–	–	– Inhibitor (strong)	UGT substrate	–
Sedative hypnotics							
Alprazolam	–	–	–	–	Substrate Inhibitor (weak)	–	–
Bromazepam	Substrate	–	–	–	Substrate (minor)	–	–
Brotizolam	–	–	–	–	Substrate	–	–
Chlordiazepoxide	–	–	–	–	Substrate	–	–
Clobazam	–	–	Substrate Inhibitor (weak)	Inhibitor (moderate)	Substrate (minor) Inducer (weak)	Substrate (P–gp)	–
Clonazepam	–	–	–	–	Substrate	–	–
Clorazepate	–	–	–	–	Substrate	–	–
Diazepam	Substrate (minor)	Substrate (minor)	Substrate Inhibitor (weak)	–	Substrate Inhibitor	–	–
Eszopiclone	–	–	–	–	Substrate	–	–
Flurazepam	–	–	–	–	Substrate	–	–
Lorazepam	–	–	–	–	–	UGT substrate	–
Lormetazepam	–	–	–	–	–	UGT substrate	–
Midazolam	–	Inhibitor (weak)	–	–	Substrate Inhibitor (weak)	–	–
Oxazepam	–	–	–	–	–	UGT substrate	–
Temazepam	–	Substrate (minor)	Substrate (minor)	–	Substrate (minor)	UGT substrate	–
Triazolam	–	–	–	–	Substrate	–	–
Zolpidem	Substrate (minor)	–	Substrate (minor)	Substrate (minor)	Substrate	–	–
Zopiclone	–	Substrate (minor)	–	–	Substrate	–	–

Data are retrieved from Smolders et al. [26] and the summary of product characteristics of the different agents for activity on CYP450 and other transporters, while data for QT prolongation were retrieved from Crediblemeds.org

CYP cytochrome P450, *OCT2* organic cation transporter 2, *MAO-I* monoamine oxidase inhibitors, *PD* pharmacodynamic, *P-gp* P-glycoprotein, *TCAs* tricyclic antidepressants, *UGT* UDP-glucuronosyltransferase, *SNRIs* serotonin-noradrenaline reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, – indicates no activity

setting, a simplification of a long-term medication regime is commonly performed, including the abrupt discontinuation of oral psychotropic agents [39]. This may significantly lower the risk of DDIs that is generally restricted only to the use of parenteral agents for sedation and treatment of delirium (e.g. midazolam, haloperidol). However, some patients may be receiving long-acting injectable antipsychotic agents to manage schizophrenia or bipolar disorder. In this scenario, clinically relevant drug interactions may occur despite ICU admission because of the long elimination half-life of the agents administered in these formulations.

Table 2 Summary of the activity of the different COVID-19 therapies on CYP450 and on transporters. Relevant PD effects (QT prolongation) of both COVID-19 agents and of severe forms of COVID-19 are indicated

Agents	Dosing schedule in COVID-19	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation	Clinical relevance
COVID-19 therapies									
Bamlanivimab	700 mg one dose	–	–	–	–	–	–	Unknown	No significant DDIs are expected according to PK/PD features of this agent
Canakinumab	450 mg one dose (weight 40–59 kg) 600 mg one dose (60–80 kg) 750 mg one dose (>80 kg)	May reverse inhibition caused by increased IL-1 levels	May reverse inhibition caused by increased IL-1 levels	May reverse inhibition caused by increased IL-1 levels	–	May reverse inhibition caused by increased IL-1 levels	–	–	Canakinumab may normalise cytochrome activity; however, no significant DDIs are expected if the dose of CYP450 substrates remained unchanged during COVID infection, and dose adjustments are required
Casirivimab-imdevimab	1200 mg/1200 mg one dose	–	–	–	–	–	–	Unknown	No significant DDIs are expected according to PK/PD features of this agent
Colchicine	LD 0.5 mg × 3/ day (days 1–7) MD 0.5 mg × 2/ day (days 8–30)	–	–	–	–	Substrate	Substrate (P-gp)	–	Consider dose reduction of 50–75% in case of concomitant administration of CYP3A4/P-gp strong inhibitors Consider dose reduction in case of moderate/severe renal or hepatic impairment caused by COVID-19

Table 2 (continued)

Agents	Dosing schedule in COVID-19	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation	Clinical relevance
Darunavir/cobicistat	800 mg/150 mg/day (up to 5–7 days)	–	–	–	Inhibitor (DAR weak) Inhibitor (COB weak)	Substrate (DAR/COB) Inhibitor (DAR) Inhibitor (COB-strong)	Inhibitor (DAR P-gp) Inhibitor (COB P-gp, BCRP, MATE1, OATP1B1/3)	–	High risk of clinically relevant DDIs in case of co-administration with CYP3A4 or P-gp substrates
Dexamethasone	6 mg/day (maximum 10 days)	–	–	–	–	Substrate inducer (moderate)	–	–	Potential DDIs are expected to be not relevant according to moderate activity on CYP3A4 as inducer
Enoxaparin	60 mg/die (weight 45–60 kg) 80 mg/die (weight 61–100 kg) 100 mg/die (weight >100 kg) (up to 14 days)	–	–	–	–	–	–	–	Consider dose reduction in case of co-administration of agents increasing risk of bleeding (SSRIs, SNRIs)
Lopinavir/ritonavir	400 mg/100 mg × 2/day (up to 14 days)	–	Inducer (weak)	Inducer (weak)	–	Substrate (LOP/RIT) Inhibitor (LOP/RIT strong)	Inducer (UGT)	Possible risk	High risk of clinically relevant DDIs in case of co-administration with CYP3A4 substrates
Remdesivir	LD 200 mg (day 1) MD 100 mg (days 2–5/10)	Inducer (in vitro)	Substrate	–	Substrate	Substrate inhibitor (in vitro) Inducer (in vitro)	Substrate (P-gp and OATP1B1) Inhibitor (OATP1B1/3) (in vitro)	Under review	Potential DDIs are expected to be not relevant due to the rapid clearance of remdesivir Substrate of CYP3A4 or OATP1B1/3 should be administered 2 hours after remdesivir infusion

Table 2 (continued)

Agents	Dosing schedule in COVID-19	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation	Clinical relevance
Ruxolitinib	5 mg × 2/day (up to 14–28 days)	–	Substrate (minor)	–	–	Substrate	Inhibitor (P-gp and BCRP)	–	Dose should be reduced of 50% in case of co-administration with strong inhibitors of CYP3A4 and 2C9. No dose reduction in case of concomitant use with weak-moderate inhibitors of CYP3A4. Dose should be increased in case of concomitant administration with strong inducers of CYP3A4
Siltuximab	11 mg/kg one dose. One additional infusion can be administered at the physician's discretion	May reverse inhibition caused by increased IL-6 levels	May reverse inhibition caused by increased IL-6 levels	May reverse inhibition caused by increased IL-6 levels	–	May reverse inhibition caused by increased IL-6 levels	–	–	Siltuximab may normalise cytochrome activity; however, no significant DDIs are expected if the dose of CYP450 substrates remained unchanged during COVID infection, and dose adjustments are required

Table 2 (continued)

Agents	Dosing schedule in COVID-19	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	Glucuronidation transporters	QT prolongation	Clinical relevance
Tocilizumab	8 mg/kg (maximum 800 mg) one dose. One additional infusion can be administered after 8–12 hours if symptoms do not improve	May reverse inhibition caused by increased IL-6 levels	May reverse inhibition caused by increased IL-6 levels	May reverse inhibition caused by increased IL-6 levels	–	May reverse inhibition caused by increased IL-6 levels	–	–	Tocilizumab may normalise cytochrome activity; however, no significant DDIs are expected if the dose of CYP450 substrates remained unchanged during COVID infection, and dose adjustments are required
Severe COVID-19		Inhibitor (weak-moderate) Caused by increased in IL-6 and IL-1 levels	Inhibitor (moderate) Caused by increased in IL-6 and IL-1 levels	Inhibitor (moderate) Caused by increased in IL-6 and IL-1 levels	–	Inhibitor (strong) Caused by increased in IL-6 and IL-1 levels	–	Possible risk	Acute kidney injury and acute liver failure caused by severe COVID-19 may impair metabolism and clearance of several agents, increasing the risk of clinically relevant DDIs

Data are retrieved from summary of product characteristics of the different agents for activity on CYP450 and other transporters, while data for QT prolongation were retrieved from Crediblemeds.org

BCRP breast cancer resistance protein, *COB* cobicistat, *CYP* cytochrome P450, *DAR* darunavir, *DDI* drug–drug interaction, *IL-1* interleukin-1, *IL-6* interleukin-6, *LD* loading dose, *LOP* lopinavir, *MATE1* multidrug and toxin extrusion 1, *MD* maintenance dose, *OATP1B1/3* organic anion transporting polypeptide 1/3, *P-gp* P-glycoprotein, *PK/PD* pharmacokinetic/pharmacodynamic, *RIT* ritonavir, *SNRIs* serotonin-norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *UGT* UDP-glucuronosyltransferase, – indicates no activity

3.4 Pharmacogenetic Issues Associated with Clinically Relevant Drug Interactions

Finally, it should not be overlooked that the genetic polymorphisms involving CYP2C19/CYP2D6 genotypes may significantly contribute by altering the disposition of some antidepressants (e.g. escitalopram, sertraline) and antipsychotic agents (e.g. aripiprazole, haloperidol, risperidone) among CYP2C19/CYP2D6 intermediate/poor and/or ultrarapid metabolisers [40]. This may potentiate the effect of COVID-19 therapies that normally are weak or moderate inhibitors or inducers of these isozymes, thus leading to clinically relevant unpredictable interactions.

4 Clinically Significant Interactions Between Psychotropic Agents and COVID-19 Therapies

Several PK DDI studies between psychotropic medications and repurposed COVID-19 exist in the literature (Tables 3, 4, 5, 6). Unfortunately, most of these studies were performed in healthy volunteers before the pandemic, whereas only a minority of case reports outlined the occurrence of clinically relevant interactions between these agents among patients with COVID-19. The extent of clinical relevance based on PD effects and the need for dose adjustments reported in these studies were highly variable. Consequently, interpretation of these findings with extrapolation to patients with COVID-19 requires caution. Several limitations of these PK studies may somewhat affect the full applicability of the reported findings in the COVID-19 scenario (e.g. lack of subjects showing underlying diseases and/or polytherapy, lack of critical acute conditions). However, they may provide useful information concerning the occurrence of clinically relevant drug interactions between psychotropic medications and repurposed COVID-19 agents.

4.1 Antidepressants

Clinically significant drug interactions between antidepressants and COVID-19 agents, mainly antiretrovirals (ritonavir and cobicistat), were reported. Overall, 12 PK studies were performed in healthy volunteers, and two case reports and one retrospective study were also identified by our search (Table 3).

In regard to SSRIs, Gutierrez et al. [41] found no significant alteration in th edisposition of escitalopram (in terms of peak concentration [C_{max}], area under the plasma concentration–time curve [AUC] and clearance [CL]) caused by concomitant administration of ritonavir in a randomised, open-label, three-way crossover study performed in 18 healthy volunteers. Conversely, Lorenzini et al. [42] described a case

of serotonin syndrome in a patient with human immunodeficiency virus (HIV) concomitantly treated with darunavir/ritonavir and escitalopram. Escitalopram serum concentrations were roughly three times as high as the upper threshold of the therapeutic range (695 nmol/L vs 250 nmol/L), potentially due to CYP3A4 and CYP2D6 inhibition caused by ritonavir. van der Lee et al. [43] found an unexpectedly decreased paroxetine exposure (1.55-fold and 1.51-fold for AUC and C_{max}, respectively) in 23 healthy volunteers concomitantly treated with fosamprenavir/ritonavir, probably related to displacement from protein binding of paroxetine resulting in higher CL, considering that both paroxetine (95%) and fosamprenavir/ritonavir (respectively 90% and 98%) are highly bound to plasma proteins. Similarly, Hanan et al. [44] found an unexpected decrease in sertraline disposition (respectively 1.49-fold and 1.36-fold for AUC and C_{max}) in 31 HIV-infected and uninfected subjects treated with ritonavir associated with different protease inhibitors (PIs), including lopinavir. The findings were attributed to induction of uridine diphosphate glucuronosyltransferase (UGT) activity. Consequently, it was concluded that higher paroxetine or sertraline dosage may be required in patients concomitantly treated with PIs and ritonavir to retain antidepressants effects. Ouellet et al. [45] found no significant alteration in ritonavir disposition among 16 healthy volunteers cotreated with the moderate CYP2D6 inhibitor fluoxetine. Consequently, it may be speculated that no lopinavir/ritonavir dose adjustments should be required in patients with mild-to-moderate COVID-19 receiving fluoxetine treatment. Finally, in a retrospective study including 575 patients affected by venous thromboembolism and treated with full-dose enoxaparin, Samuel and Seifert [46] reported a higher risk of major bleeding in subjects treated with escitalopram compared with those receiving other SSRIs or no antidepressant therapy. This is probably due to the well-known increased risk of bleeding associated with SSRIs and resulting in additive PD toxicity [47].

Among serotonin-noradrenaline reuptake inhibitors, only one case report of interaction with COVID-19 agents was reported. Mas Serrano et al. [48] described a case of serotonin syndrome in a patient receiving lopinavir/ritonavir for COVID-19 pneumonia and concomitantly treated with duloxetine and lithium. The syndrome was attributed to the inhibitory effect of ritonavir on CYP2D6, but unfortunately a PK analysis and/or therapeutic drug monitoring (TDM) of duloxetine were not performed. However, a PD interaction also could not be ruled out.

Among TCAs, clinically significant drug interactions with repurposed agents for COVID-19 were documented in healthy volunteers only for desipramine. Mascolini et al. [49] found a moderate increase in desipramine disposition (58–65% and 24% for AUC and C_{max}, respectively) in nine healthy subjects concomitantly treated with cobicistat.

Table 3 Pharmacokinetic interactions between repurposed COVID-19 therapies and antidepressants according to clinical studies or case reports in non-COVID19 subjects

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Mascolini et al. (2011) [49]	Phase II: healthy volunteers (9)	Cobicistat 150 mg/day PO for 10 days	Desipramine PO on day 10 (dose not provided)	Inhibition of CYP2D6	58-65% ↑ AUC 24% ↑ C_{max}	Not reported	Limited clinical significance (increasing in AUC <2-fold) Consider lower initial or maintenance dose of desipramine	Although coadministration of desipramine and darunavir/cobicistat in mild COVID-19 could occur, the use of desipramine as an antidepressant is limited
Park et al. (2010) [52]	Healthy volunteers (44), sequential treatment	Ritonavir 300 mg × 2/day PO on days 8–10 Ritonavir 400 mg × 2/day PO on days 11–13 Ritonavir 500 mg × 2/day PO on days 14–16 Ritonavir 300 mg × 2/day PO on days 17–30	Bupropion XL 150 mg PO on day 1 Bupropion XL 150 mg PO on day 24	Induction of CYP2B6 and UGT	66% ↓ AUC 62% ↓ C_{max}	Not reported	Consider higher bupropion dose if antidepressant treatment is deemed ineffective	In mild/moderate COVID-19, high ritonavir dose (>100 mg × 2/day) is not used
Park et al. (2010) [52]	Phase I: healthy volunteers (20), sequential treatment	Ritonavir 100 mg × 2/day PO on days 8–30	Bupropion XL 150 mg PO on day 1 Bupropion XL 150 mg PO on day 24	Induction of CYP2B6 and UGT	22% ↓ AUC 21% ↓ C_{max}	Not reported	Limited clinical significance	In mild/moderate COVID-19, the low ritonavir dose (100 mg × 2/day) should not significantly affect bupropion exposure
Hogeland et al. (2007) [53]	Phase I: healthy volunteers (12), open-label sequential	Lopinavir/ritonavir 400/100 mg × 2/day PO on days 15–29 Lopinavir/ritonavir 400/100 mg PO on day 30	Bupropion XL 100 mg PO on day 1 Bupropion XL 100 mg PO on day 30	Induction of CYP2B6 and UGT	57% ↓ AUC 57% ↓ C_{max} 32% ↓ $t_{1/2}$	Not reported	Consider higher bupropion dose if antidepressant treatment is deemed ineffective	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause a moderate reduction in bupropion exposure

Table 3 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Kharasch et al. (2008) [54]	Healthy volunteers (13), three-session sequential crossover	Ritonavir 200 mg × 3/day PO on day 1 Ritonavir 300 mg × 2/day PO on days 2–7 Ritonavir 400 mg × 2/day PO on days 8–18	Bupropion 150 mg PO on days 1, 4 and 17	Induction of CYP2B6 and UGT	16% $\downarrow$ AUC (acute) 33% $\downarrow$ AUC (chronic) 1.2-fold $\uparrow$ CL (acute) 1.4-fold $\uparrow$ CL (chronic)	Not reported	Consider higher bupropion dose if antidepressant treatment is deemed ineffective	In mild/moderate COVID-19, the low ritonavir dose (100 mg × 2/day) should not significantly affect bupropion exposure
Hesse et al. (2006) [55]	Healthy volunteers (7), crossover vs placebo	Ritonavir 200 mg × 2/day PO on days 1–2	Bupropion 75 mg PO on day 2	Induction of CYP2B6 and UGT	$\downarrow$ AUC, $\downarrow t_{1/2}$, $\uparrow$ CL <20%	Not reported	Limited clinical significance	In mild/moderate COVID-19, the low ritonavir dose (100 mg × 2/day) and short duration of treatment should not significantly affect bupropion exposure
Aarnoutse et al. (2005) [50]	Healthy volunteers (13), open-label, one-arm, two-period, fixed-order	Ritonavir 100 mg × 2/day PO on days 6–25	Desipramine 50 mg PO on days 1 and 22	Inhibition of CYP2D6	1.26-fold $\uparrow$ AUC 1.3-fold $\uparrow t_{1/2}$ 1.2-fold $\downarrow$ CL	Not reported	Limited clinical significance	Although coadministration of desipramine and lopinavir/ritonavir in mild COVID-19 could occur, the use of desipramine as an antidepressant is limited and no dose adjustments are required
Mas Serrano et al. (2020) [48]	COVID-19 pneumonia, case report (1)	Lopinavir/ritonavir 400/100 mg × 2/day PO	Duloxetine 120 mg/day PO Lithium 800 mg/day PO	Inhibition of CYP2D6	Not reported	Serotonin syndrome	Close monitoring for occurrence of serotonin syndrome in patients treated with SSRIs/SNRIs and strong inhibitor of CYP450	Hepatic or renal impairment caused by COVID-19 could further affect antidepressant metabolism and clearance

Table 3 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Gutierrez et al. (2003) [41]	Healthy volunteers (18), randomised, open-label, three-way crossover	Ritonavir 600 mg PO single dose on days 15 and 29	Escitalopram 20 mg PO single dose on days 1 and 29	Inhibition of CYP3A4	1.08-fold $\uparrow$ AUC 1.07-fold $\uparrow T_{max}$ 1.11-fold $\downarrow$ CL 1.05-fold $\downarrow t_{1/2}$ 1.03-fold $\downarrow C_{max}$	Not reported	No clinical significance	In mild/moderate COVID-19, the low ritonavir dose (100 mg × 2/day) should not significantly affect escitalopram exposure
Lorenzini et al. (2012) [42]	HIV infection, case report (1)	Darunavir/ritonavir 600/100 mg × 2/day PO	Escitalopram 10 mg × 2/day PO	Inhibition of CYP3A4 and 2D6	Escitalopram serum levels 695 nmol/L vs expected therapeutic range of 40–250 nmol/L CYP2D6 poor metaboliser and 2C19 intermediate metaboliser	Serotonin syndrome	Close monitoring for occurrence of serotonin syndrome in patients treated with SSRIs/SNRIs and strong inhibitor of CYP450 Decreased activity of CYP450 isoenzymes due to pharmacogenetic alterations should be considered	Hepatic or renal impairment caused by COVID-19 could further affect antidepressant metabolism and clearance Decreased activity of CYP450 isoenzymes due to pharmacogenetic alterations should be considered
Ouellet et al. (1998) [45]	Phase I: healthy volunteers (16), open-label	Ritonavir 600 mg PO single dose on days 1 and 10	Fluoxetine 30 mg × 2/day PO on days 3–10	Inhibition of CYP2D6	1.19-fold $\uparrow$ AUC of ritonavir	Not reported	Limited clinical significance No ritonavir dose adjustments are required	In mild/moderate COVID-19, the exposure of low ritonavir dose (100 mg × 2/day) should not significantly be affected by fluoxetine The use of lopinavir/ritonavir in COVID-19 is currently limited by poor evidence of efficacy

Table 3 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
van der Lee et al. (2007) [43]	Healthy volunteers (23), open-label, multiple-dose, two-arm, two-sequence, two-period	Fosamprenavir/ritonavir 700/100 mg × 2/day PO on days 28–37	Paroxetine 20 mg/day PO on days 1–10 and 28–37	Displacement of protein binding of paroxetine by fosamprenavir and/or ritonavir	1.55-fold ↓ AUC; 1.25-fold ↑ $t_{1/2}$; 1.51-fold ↓ C_{max}	Not reported	The unexpected findings (according to CYP450 pathways) of decreased paroxetine exposure could be clinically relevant. Higher dose of paroxetine may be necessary to accomplish the needed antidepressant effect	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in paroxetine exposure
Hanan et al. (2019) [44]	HIV-infected and uninfected subjects (31), three arms	PI/ritonavir PO for at least 4 weeks. Dose not specified	Sertraline 100 mg/day PO for at least 14 days	Induction of UGT Polymorphisms in CYP450 isoenzymes	1.49-fold ↓ AUC; 1.36-fold ↓ C_{max}; 1.14-fold ↑ CL	Not reported	The unexpected findings (according to CYP450 pathways) of decreased sertraline exposure could be clinically relevant. Modestly higher dose of sertraline may be necessary to accomplish the needed antidepressant effect	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause moderate reduction in sertraline exposure
Greenblatt et al. (2003) [56]	Healthy volunteers (10), randomised, four-way crossover	Ritonavir 200 mg × 2/day PO on days 1–2	Trazodone 50 mg PO on day 2	Inhibition of CYP3A4	2.37-fold ↑ AUC; 1.34-fold ↑ C_{max}; 2.22-fold ↑ $t_{1/2}$; 2.07-fold ↓ CL; 1.12-fold ↓ T_{max}	Significant impairment of psychomotor performance and increased sedation	Coadministration should be avoided or trazodone dose should be reduced by 50–75%	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant increase in trazodone exposure

Table 3 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Samuel et al. (2016) [46]	Patients affecting by VTE (575), retrospective cohort study	Enoxaparin > 1 mg/kg × 2/day or > 1.5 mg/kg/day SC	SSRIs at labelled dose PO	Synergistic PD toxicity	Not reported	Elevated risk of major bleeding reported in patients on escitalopram compared with those on any of the other SSRIs or patients not on SSRIs (46.2% vs 15.2% and 17.0%, respectively, $p = 0.018$)	Close monitoring for occurrence of major bleeding in patients treated with SSRIs and full-dose enoxaparin	In moderate/severe COVID-19, enoxaparin is currently use at intermediate dosage. Risk of major bleeding could be reduced compared to full-dose enoxaparin administration

AUC area under the concentration–time curve, *CL* clearance, C_{max} peak concentration, *CYP* cytochrome P450, *HIV* human immunodeficiency virus, *PI* protease inhibitor, *PD* pharmacodynamic, *PO* orally, *SC* subcutaneous, *SNRIs* serotonin-noradrenaline reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, $t_{1/2}$ half-life, T_{max} time to reach peak concentration, *UGT* uridine diphosphate glucuronosyltransferase, *VTE* venous thromboembolism, *XL* extended-release, ↓ decreased, ↑ increased

Table 4 Pharmacokinetic interactions between repurposed COVID-19 therapies and antipsychotic agents according to clinical studies or case reports in non-COVID19 subjects

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Hahn et al. (2016) [61]	Patient with HIV with bipolar disorder (1), case report	Lopinavir/ritonavir 400/100 mg × 2/ day PO	Aripiprazole 200 mg IM + 5 mg/ day PO	Ultrarapid metaboliser for CYP2D6	Aripiprazole serum levels 94 ng/mL vs expected therapeutic range of 150–500 ng/mL	Clinical worsening and relapse of depressive mood disorder	The unexpected findings (according to CYP450 pathways) of decreased aripiprazole exposure could be clinically relevant. Variation in activity of CYP450 isoenzymes due to pharmacogenetic alterations should be considered	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause moderate reduction in aripiprazole exposure when concomitant pharmacogenetic alterations exist. TDM or pharmacogenetic analysis should be performed in case of ineffective treatment
Aung et al. (2010) [60]	Patient with HIV with depressive disorder (1), case report	Darunavir/ritonavir 800/100 mg/day PO	Aripiprazole 50 mg/day PO	Inhibition of CYP3A4 and 2D6	Aripiprazole serum levels 1100 ng/mL	Confusion and loss of coordination	Coadministration should be avoided or aripiprazole dose should be reduced by 50-80%	TDM coupled with pharmacogenetic analysis for polymorphisms of CYP2D6 should be considered in patients with mild/moderate COVID-19 during treatment with lopinavir/ritonavir

Table 4 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Jacobs et al. (2014) [59]	Healthy volunteers (20), open-label, randomised, two-period, cross-over	Fosamprenavir/ritonavir 700/100 mg × 2/day PO on days 1–16	Olanzapine 15 mg PO on day 13; Olanzapine 10 mg PO on day 48	Induction of CYP1A2 and UGT	1.00-fold = AUC; 1.32-fold ↑ C_{max}; 1.32-fold ↓ $t_{1/2}$	Not reported	Olanzapine dose should be increased by 50% (15 mg/day instead of scheduled 10 mg/day)	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in olanzapine exposure. Higher dose of olanzapine should be considered
Penzak et al. (2002) [58]	Healthy volunteers (14), open-label	Ritonavir 300 mg × 2/day PO on days 15–17; Ritonavir 400 mg × 2/day PO on days 18–21; Ritonavir 500 mg × 2/day PO on days 22–25	Olanzapine 10 mg PO on days 1 and 26	Induction of CYP1A2 and UGT	2.13-fold ↓ AUC; 1.67-fold ↓ C_{max}; 2.00-fold ↓ $t_{1/2}$; 2.15-fold ↑ CL	Not reported	Olanzapine dose should be increased by 50% (15 mg/day instead of scheduled 10 mg/day)	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in olanzapine exposure. Higher dose of olanzapine should be considered
Pollack et al. (2009) [62]	Patients with HIV with bipolar and anxiety disorders (2), case series	Atazanavir/ritonavir 300/100 mg/day PO	Quetiapine 400 mg/day PO (case 1); Quetiapine 600 mg/day PO (case 2)	Inhibition of CYP3A4	Not performed	Increased appetite and weight gain Hyperglycaemia Increased sedation and worsened mental confusion	Coadministration should be avoided	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant increase in quetiapine exposure and severe adverse events Replace quetiapine with olanzapine

Table 4 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Geraci et al. (2010) [63]	Patient with HIV with schizoaffective disorder (1), case report	Lopinavir/ritonavir 200/50 mg × 2/day PO	Quetiapine 900 mg/day PO Perphenazine 8 mg/day PO	Inhibition of CYP3A4 and 2D6 with prolonged α-adrenergic blockade	Not reported	Low-flow priapism requiring emergency department admission	Coadministration should be avoided	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant increase in quetiapine exposure and severe adverse events Replace quetiapine with olanzapine
Kelly et al. (2002) [65]	Patient with HIV with tic disorder (1), case report	Indinavir/ritonavir 800/200 mg × 2/day PO	Risperidone 2 mg × 2/day PO increased to 3 mg × 2/day PO	Inhibition of CYP3A4 and CYP2D6	Not reported	Extrapyramidal symptoms	Close monitoring for occurrence of serious adverse events in patients treated with antipsychotic agents and strong inhibitor of CYP450	Hepatic or renal impairment caused by COVID-19 could further affect antipsychotic metabolism and clearance
Jover et al. (2002) [66]	Patient with HIV with manic behaviour (1), case report	Indinavir/ritonavir 400/200 mg × 2/day PO	Risperidone 3 mg × 2/day PO	Inhibition of CYP3A4 and CYP2D6	Not reported	Profound coma	Close monitoring for occurrence of serious adverse events in patients treated with antipsychotic agents and strong inhibitor of CYP450 Coadministration should be avoided or risperidone dose should be reduced at least by 50%	Hepatic or renal impairment caused by COVID-19 could further affect antipsychotic metabolism and clearance

Table 4 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Mas Serrano et al. (2020) [48]	Mild COVID-19 pneumonia (1), case report	Lopinavir/ritonavir 400/100 mg × 2/ day PO	Risperidone 1 mg × 2/day PO on days 10–11	Inhibition of CYP3A4 and CYP2D6	Not reported	Serotonin syndrome	Close monitoring for occurrence of serotonin syndrome in patients treated with antipsychotic agents and strong inhibitor of CYP450	Hepatic or renal impairment caused by COVID-19 could further affect antipsychotic metabolism and clearance
Gonzalez et al. (2016) [67]	Patients with HIV with schizoaffective disorders (3), case series	Darunavir/ritonavir PO dose not specified (case 1–3) Lopinavir/ritonavir dose not specified (case 2)	Risperidone 2 mg × 2/day PO (case 1–2) Risperidone 3 mg × 2/day PO (case 3)	Inhibition of CYP3A4 and CYP2D6	Not reported	Late-onset angioedema	Close monitoring for occurrence of serious adverse events in patients treated with antipsychotic agents and strong inhibitor of CYP450	Hepatic or renal impairment caused by COVID-19 could further affect antipsychotic metabolism and clearance
Lee et al. (2000) [68]	Patient with HIV with psychotic disorder (1), case report	Ritonavir 400 mg/ day PO on day 4	Risperidone 0.5 mg/day on day 1 Risperidone 1 mg/ day on day 2 Risperidone 1.5 mg/day on day 3	Inhibition of CYP3A4 and CYP2D6	Not reported	Neuroleptic malignant syndrome	Close monitoring for occurrence of neuroleptic malignant syndrome in patients treated with antipsychotic agents and strong inhibitor of CYP450	Hepatic or renal impairment caused by COVID-19 could further affect antipsychotic metabolism and clearance

AUC area under the concentration–time curve, *CL* clearance, *C$_{max}$* peak concentration, *CYP* cytochrome P450, *HIV* human immunodeficiency virus, *IM* intramuscular, *PD* pharmacodynamic, *PO* orally, *TDM* therapeutic drug monitoring, *t$_{1/2}$* half-life, *UGT* uridine diphosphate glucuronosyltransferase, ↑ increased, ↓ decreased

Table 5 Pharmacokinetic interactions between repurposed COVID-19 therapies and mood stabilisers according to clinical studies or case reports in non-COVID19 subjects

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Mateu de-Antonio et al. (2001) [74]	Patient with HIV with seizure (1), case report	Ritonavir 300 mg × 2/day PO	Carbamazepine 400 mg × 3/day PO	Inhibition of CYP3A4	Carbamaz-epine exposure increased by 99% (16.6 mg/L vs 8.3 mg/L)	Vertigo, drowsi-ness, disorienta-tion, diplopia and severe ataxia	Coadministration should be avoided or carbamazepine dose should be reduced at least by 50% TDM should be performed	Hepatic or renal impairment caused by COVID-19 could further affect carbamazepine metabolism and clearance
Bates et al. (2006) [75]	Patient with HIV with seizure (1), case report	Lopinavir/ritonavir 400/100 mg × 2/day PO	Carbamazepine 400 mg × 3/day PO	Inhibition of CYP3A4	Carbamaz-epine exposure increased by 46% (15.0 mg/L vs 10.3 mg/L)	Excessive drowsi-ness	Coadministration should be avoided or carbamazepine dose should be reduced at least by 33–50% TDM should be performed	Hepatic or renal impairment caused by COVID-19 could further affect carbamazepine metabolism and clearance
Garcia et al. (2000) [76]	Patient with HIV with seizure and multifocal leu-koencephalopathy (1), case report	Ritonavir 600 mg × 2/day PO	Carbamazepine 600 mg/day PO	Inhibition of CYP3A4	Carbamaz-epine exposure increased by 22% (18.0 mg/L vs 14.7 mg/L)	Dizziness and a progressive gait disorder	Coadministration should be avoided or carbamazepine dose should be reduced at least by 50% TDM should be performed	Hepatic or renal impairment caused by COVID-19 could further affect carbamazepine metabolism and clearance
Kato et al. (2000) [77]	Patient with HIV with epilepsy (1), case report	Ritonavir 200 mg × 3/day PO	Carbamazepine 350 mg × 2/day PO	Inhibition of CYP3A4	Carbamaz-epine exposure increased by 87% (17.8 mg/L vs 9.5 mg/L)	Vomiting, vertigo, and transient liver dysfunction	Coadministration should be avoided or carbamazepine dose should be reduced at least by 50% TDM should be performed	Hepatic or renal impairment caused by COVID-19 could further affect carbamazepine metabolism and clearance

Table 5 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Burman et al. (2000) [78]	Patient with HIV with general seizure (1), case report	Ritonavir 400 mg × 2/day PO	Carbamazepine 600 mg/day PO	Inhibition of CYP3A4	Carbamazepine exposure increased by 295% (20.4 mg/L vs 6.9 mg/L)	Worsening ataxia	Coadministration should be avoided or carbamazepine dose should be reduced at least by 50% TDM should be performed	Hepatic or renal impairment caused by COVID-19 could further affect carbamazepine metabolism and clearance
Burger et al. (2008) [72]	Healthy volunteers (18), open-label, sequential, three-period, single-center, phase IV, multiple-dose	Atazanavir 400 mg/day PO on days 8–17 Atazanavir/ritonavir 300/100 mg/day PO on days 18–32	Lamotrigine 100 mg PO on days 1, 13 and 27	Induction of UGT	32% ↓ AUC 6% ↓ C_{max} 27% ↓ $t_{1/2}$	Not reported	Moderate reduction in lamotrigine exposure with atazanavir/ritonavir Lamotrigine dose should be increased by 50%	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in lamotrigine exposure Higher dose of lamotrigine coupled with TDM should be considered
van der Lee et al. (2006) [73]	Healthy volunteers (18), open-label, sequential, 3-period, single-center, phase IV, multiple-dose	Lopinavir/ritonavir 400/100 mg × 2/day on days 11–23	Lamotrigine 50 mg/day PO on days 1–2 Lamotrigine 100 mg × 2/day PO on days 3–23	Induction of UGT	50% ↓ AUC 44% ↓ C_{min} 46% ↓ C_{max} 46% ↓ $t_{1/2}$ 98% ↑ CL	Not reported	Significant reduction in lamotrigine exposure Lamotrigine dose should be increased by 50–200%	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in lamotrigine exposure Higher dose of lamotrigine coupled with TDM should be considered

Table 5 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
DiCenzo et al. (2004) [79]	Patients with HIV (8), three arms	Lopinavir/ritonavir 400/100 mg × 2/day PO for at least 4 weeks	Valproate 250 mg × 2/day PO on days 1–7	Inhibition of CYP450	1.75-fold ↑ AUC lopinavir 1.09-fold ↑ $t_{1/2}$ lopinavir 1.33-fold ↑ C_{max} lopinavir	Not reported	Moderate increase in lopinavir exposure No significant effect of lopinavir/ritonavir on valproate exposure	In mild/moderate COVID-19, the exposure of low ritonavir dose (100 mg × 2/day) should not significantly be affected by valproate The use of lopinavir/ritonavir in COVID-19 is currently limited by poor evidence of efficacy
Sheenan et al. (2006) [80]	Patient with HIV with bipolar disorder (1), case report	Lopinavir/ritonavir 400/100 mg × 2/day PO	Valproate 250 mg × 3/day PO	Induction of UGT	Valproate exposure decreased by 48% (238 vs 495 μmol/L)	Worsen manic symptoms	Valproate dose should be increased by 50%	In mild/moderate COVID-19, lopinavir/ritonavir at usual dose (400/100 mg × 2/day) may cause significant reduction in valproate exposure Higher dose of valproate coupled with TDM should be considered
Mas Serrano et al. (2020) [48]	COVID-19 pneumonia (1), case report	Lopinavir/ritonavir 400/100 mg × 2/day PO	Duloxetine 120 mg/day PO Lithium 800 mg/day PO	Inhibition of CYP2D6 Synergistic PD toxicity between increased duloxetine exposure and lithium	Not performed	Serotonin syndrome	Close monitoring for occurrence of serotonin syndrome in patients treated with lithium and strong inhibitor of CYP450	Renal impairment caused by COVID-19 could further affect lithium clearance

AUC area under the concentration–time curve, *CL* clearance, C_{max} peak concentration, C_{min} trough concentration, *CYP* cytochrome P450, *HIV* human immunodeficiency virus, *PD* pharmacodynamic, *PO* orally, *TDM* therapeutic drug monitoring, $t_{1/2}$ half-life, T_{max} time to reach peak concentration, *UGT* uridine diphosphate glucuronosyltransferase, ↑ increased, ↓ decreased

Table 6 Pharmacokinetic interactions between repurposed COVID-19 therapies and sedative hypnotics according to clinical studies or case reports in non-COVID19 subjects

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Villikka et al. (1998) [85]	Healthy volunteers (10), randomised, double-blind, cross-over	Dexamethasone 1.5 mg/day PO on days 1–4	Triazolam 0.5 mg on day 5	Induction of CYP3A4	$19\% \downarrow$ AUC $11\% \downarrow C_{max}$	No difference in psychomotor tests	Limited clinical significance No triazolam dose adjustments are required	In moderate/severe COVID-19, the higher dosage of dexamethasone (6 mg/day up to 7 days) should not significantly affect benzodiazepine exposure
Zhuang et al. (2015) [87]	Patients affected by rheumatoid arthritis and CRP ≥ 8.0 mg/L (12), open-label, phase I	Sirukumab 300 mg SC on day 8	Midazolam 0.03 mg/kg PO on days 1, 15, 29 and 50	Reversion of IL-6-mediated suppression of CYP3A	$30–35\% \downarrow$ AUC $23–34\% \downarrow C_{max}$	Not reported	Significant reduction in midazolam exposure Midazolam dose should be increased by 30–50%	In severe COVID-19 with cytokine storm and high IL-6 level, tocilizumab or siltuximab (acting similarly to sirukumab) could significantly affect midazolam exposure Higher midazolam dosage should be required after administration of anti-IL-6 agents for adequate sedation

Table 6 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Mathias et al. (2010) [89]	Healthy volunteers (72), double-blind and double-dummy	Cobicistat 50–200 mg/day PO on days 2–15	Midazolam 5 mg PO on days 1 and 15	Inhibition of CYP3A4	9.8–19.0-fold ↑ AUC 3.1–3.9-fold ↑ C_{max} 1.7–3.7-fold ↑ $t_{1/2}$ 9.0–20.1-fold ↓ CL	Not reported	Significant increase in midazolam exposure Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19
Menon et al. (2015) [91]	Healthy volunteers (12), open-label, phase I	Paritaprevir/ritonavir 150/100 mg PO	Alprazolam 0.5 mg PO Zolpidem 5 mg PO	Inhibition of CYP3A4	Alprazolam: 34% ↑ AUC 9% ↑ C_{max} Zolpidem: 6% ↓ AUC 6% ↓ C_{max}	Not reported	Moderate increase in alprazolam exposure Coadministration should be avoided or alprazolam dosage should be reduced	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting

Table 6 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Greenblatt et al. (2000) [90]	Healthy volunteers (10), double-blind, randomised, two-way, crossover	Ritonavir 200 mg × 2/day PO on days 1–2	Alprazolam 1 mg PO after the second dose of ritonavir	Inhibition of CYP3A4	2.48-fold ↑ AUC 1.04-fold ↑ C_{max} 1.5-fold ↑ T_{max} 2.23-fold ↑ $t_{1/2}$ 2.37-fold ↓ CL	Increase in sedation and performance impairment	Significant increase in alprazolam exposure Coadministration should be avoided or alprazolam dosage should be reduced	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative-hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting
Schmitt et al. (2009) [92]	Healthy volunteers (18), prospective, open-label, one-sequence, two-period, crossover	Saquinavir/ritonavir 1000/100 mg × 2/day on days 2–15	Midazolam 7.5 mg PO on days 1 and 16	Inhibition of CYP3A4	12.44-fold ↑ AUC 4.27-fold ↑ C_{max} 3.19-fold ↑ $t_{1/2}$ 12.44-fold ↓ CL	Prolonged sedation	Significant increase in midazolam exposure Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative-hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19

Table 6 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Greenblatt et al. (2009) [93]	Healthy volunteers (13), three-way crossover	Ritonavir 300 mg PO	Midazolam 3 mg PO	Inhibition of CYP3A4	26.41-fold ↑ AUC 3.96-fold ↑ C_{max} 8.77-fold ↑ $t_{1/2}$ 25.11-fold ↓ CL	Not reported	Significant increase in midazolam exposure Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative-hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19
Eichbaum et al. (2013) [94]	Healthy volunteers (12), open, fixed-sequence	Ritonavir 0.1–300 mg PO	Midazolam 3 mg PO	Inhibition of CYP3A4	1.17–9.01-fold ↑ AUC 1.21–10.5-fold ↓ CL	Not reported	Significant increase in midazolam exposure Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19

Table 6 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Hafner et al. (2010) [95]	Healthy volunteers (12), open, fixed-sequence, two-group design	Ritonavir 300 mg × 2/day PO plus St John's wort 300 mg × 3/day PO on days 1–14	Midazolam 4 mg PO or 2 mg IV after 6 hours on day 15	Inhibition of CYP3A4	Oral midazolam: 5.39-fold ↑ AUC 2.24-fold ↑ C_{max} 1.62-fold ↑ $t_{1/2}$ 16.30-fold ↓ CL IV midazolam: 3.02-fold ↑ AUC 1.15-fold ↑ C_{max} 1.72-fold ↑ $t_{1/2}$	Not reported	Significant increase in midazolam exposure, more pronounced for oral vs intravenous administration Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19
Hsu et al. (2012) [96]	Patients with HIV undergoing bronchoscopy (241), retrospective cohort	PI/ritonavir PO according to physician's decision	Midazolam IV (median dose 4 mg)	Inhibition of CYP3A4	Not reported	Severe prolonged sedation was 9.80% in the exposed group vs 1.58% in the nonexposed group (relative risk 6.21, 95% confidence interval 1.53–25.12)	Significant increase in midazolam exposure Coadministration should be avoided or consider use of midazolam IV only in ICU setting with close monitoring of patients	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative-hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting Use of midazolam IV is unlikely in mild/moderate COVID-19

Table 6 (continued)

Study and year of publication	Study population and design (N of patients)	COVID-19 agent and dosage	Psychotropic agent and dosage	Mechanism	Pharmacokinetic effect	Pharmacodynamic effect	Clinical relevance	Applicability to COVID-19 setting (according to severity of disease and clinical scenario)
Greenblatt et al. (2000) [97]	Healthy volunteers (6), double-blind, randomised, five-way crossover design	Ritonavir 200 mg × 2/day PO on days 1–2	Triazolam 0.125 mg PO or zolpidem 5 mg PO on day 2	Inhibition of CYP3A4	Triazolam: 20.39-fold ↑ AUC 1.87-fold ↑ C_{max} 1.8-fold ↑ T_{max} 13.67-fold ↑ $t_{1/2}$ 26.45-fold ↓ CL Zolpidem: 1.28-fold ↑ AUC 1.22-fold ↑ C_{max} 1.13-fold ↓ T_{max} 1.2-fold ↑ $t_{1/2}$ 1.35-fold ↓ CL	Increased sedation and impairment of psychomotor performance	Significant increase in triazolam exposure Coadministration should be avoided	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting
Culm-Merdek et al. (2006) [98]	Healthy volunteers (23), open, fixed-sequence, three-group design	Ritonavir 200 mg × 2/day PO on days 2–11	Triazolam 0.1875 mg PO on days 1, 3, 11, 15	Inhibition of CYP3A4	21.1-fold ↑ AUC 2.73-fold ↑ C_{max} 13.48-fold ↑ $t_{1/2}$ 23.93-fold ↓ CL	Not reported	Significant increase in triazolam exposure Coadministration should be avoided	In mild/moderate COVID-19, concomitant use of darunavir/cobicistat or lopinavir/ritonavir with sedative-hypnotics metabolised by CYP3A4 should be avoided Prefer oxazepam-like agents in outpatient setting

AUC area under the concentration–time curve, *CL* clearance, C_{max} peak concentration, *CRP* C-reactive protein, *CYP* cytochrome P450, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *IL-6* interleukin-6, *IV* intravenously, *PI* protease inhibitors, *PO* orally, *SC* subcutaneously, *TDM* therapeutic drug monitoring, $t_{1/2}$ half-life, T_{max} time to reach peak concentration, *UGT* uridine diphosphate glucuronosyltransferase, ↓ decreased, ↑ increased

Similarly, Aarnoutse et al. [50] found a slight increase in desipramine exposure (1.26-fold in AUC) and decreased CL among 13 healthy volunteers concomitantly receiving ritonavir. The findings could be due to cobicistat- and/or ritonavir-mediated CYP2D6 inhibition and should prompt lowering of the initial or maintenance dose of desipramine in patients receiving cotreatment with these PIs. However, given the current limited use of desipramine and other TCAs as first-line treatment for depression, the relevance of these PK interactions in the COVID-19 setting is expected currently to be of limited interest [51].

Five PK studies assessed in healthy volunteers the impact of ritonavir alone and/or in combination with lopinavir on bupropion exposure [52–55]. Consistent findings were found in terms of decreased bupropion disposition, from 20 to 62–66% for C_{max} and AUC, respectively, possibly due to induction of CYP2B6 and UGT enzymes caused by ritonavir. Consequently, a higher bupropion dosage could be appropriate in patients with COVID-19 concomitantly treated with lopinavir/ritonavir whenever antidepressant treatment is deemed ineffective.

Greenblatt et al. [56] found a significant increase in trazodone exposure (respectively 2.37-fold and 2.22-fold in AUC and half-life) coupled with a 2.07-fold decreased CL among ten healthy subjects concomitantly receiving ritonavir, possibly resulting from strong inhibitory activity on CYP3A4. A significant impairment of psychomotor performance and increased sedation were also reported. Consequently, it was recommended that the coadministration of trazodone and PIs/ritonavir should be avoided or the trazodone dose should be reduced by 50–75%.

No other PK DDI between antidepressants and COVID-19 agents has been studied. However, based on the PK/PD properties of the different medications, it may be speculated that some clinically relevant interactions might occur. Predicted DDIs and their potential risk are summarised in Table 1 of the Electronic Supplementary Material (ESM). No further high-risk PK or PD interactions between antidepressants and COVID-19 therapies can be predicted. For lopinavir/ritonavir and for darunavir/cobicistat, a moderate risk of relevant PK interactions (higher exposure of antidepressants metabolised by CYP3A4 and CYP2D6 requiring dose adjustments) and PD (QT prolongation with concomitant administration of lopinavir/ritonavir and several SSRIs, TCAs, mianserin, mirtazapine, or trazodone) interactions could be predicted. In patients affected by a cytokine storm and treated with anti-IL-6 and/or anti-IL-1 agents such as tocilizumab, siltuximab and canakinumab, an upregulation of CYP3A4 activity may be expected [57]. Consequently, for antidepressants that are metabolised by CYP3A4, it might be necessary to increase the dosage for ensuring efficacy, even if the magnitude of this increase is difficult to predict a priori. However, it should be mentioned that anti-IL-6 and IL-1

agents are used in patients with moderate-to-severe COVID-19 admitted to the ICU in which oral antidepressants are usually stopped. No clinically relevant interactions involving remdesivir, colchicine, ruxolitinib, dexamethasone, bamlanivimab and casirivimab/imdevimab are expected to occur with antidepressants.

Overall, according to real-world evidence and PK/PD properties, lopinavir/ritonavir and darunavir/cobicistat pose the major concerns for the occurrence of clinically relevant interactions with antidepressants. Higher exposure may occur for TCAs, serotonin-noradrenaline reuptake inhibitors (except duloxetine), SSRIs (except sertraline and vortioxetine) and other antidepressants (except milnacipran). A significant decrease in bupropion exposure was reported. However, no antidepressant should be a priori avoided in the case of concomitant administration with PIs. The use of agents showing a low risk of PK/PD interactions (e.g. sertraline, vortioxetine, milnacipran) should be preferred.

4.2 Antipsychotic Agents

Clinically significant drug interactions between antipsychotic agents and COVID-19 agents, especially with ritonavir-boosted PIs, were documented in healthy volunteers and in patients without COVID-19. Overall, two PK studies and nine case reports were identified by our search (Table 4). None of these involved first-generation antipsychotic agents.

Penzak et al. [58] found a significant decrease in olanzapine exposure (respectively 2.13-fold and 1.67-fold in AUC and C_{max}) coupled with increased CL (2.15-fold) in 14 healthy volunteers concomitantly treated with ritonavir, probably due to CYP1A2 and UGT induction. Consequently, a 50% dosage increase of olanzapine (15 mg/day instead of scheduled 10 mg/day) was suggested in patients cotreated with ritonavir-boosted PIs. These findings were also confirmed by Jacobs et al. [59] in a PK study performed in 20 healthy subjects concomitantly treated with fosamprenavir/ritonavir and olanzapine. No significant difference in olanzapine exposure was found when concomitantly administered with fosamprenavir/ritonavir (at a dosage of 15 mg/day) or used alone (at a dosage of 10 mg/day), thus proving the need for increasing olanzapine dose.

Aung et al. [60] described a case of aripiprazole toxicity (resulting in confusion and loss of motor coordination) in a patient with HIV treated with darunavir/ritonavir and affected by depressive disorder. The aripiprazole serum level was more than two times higher than the upper threshold of the desired range (1100 ng/mL vs 500 ng/mL). This was attributed to the inhibitory activity of ritonavir on CYP3A4- and CYP2D6-mediated metabolism of aripiprazole and called for an aripiprazole TDM-based dose adjustment (reduction by 50–80%), or avoidance of coadministration. Interestingly, opposite findings were

reported by Hahn and Roll [61] in a patient with HIV affected by bipolar disorder who experienced a relapse of mood disorder associated with an aripiprazole (both oral and intramuscular depot formulations) serum concentration below the therapeutic range (94 ng/mL vs 150–500 ng/mL) during cotreatment with lopinavir/ritonavir. The findings were attributed to the patients' status of extensive or ultrarapid metaboliser of CYP2D6 that was able to overcome the inhibition of CY2D6 and 3A4 activity promoted by ritonavir. It was concluded that TDM coupled with a pharmacogenetic analysis may be helpful in tailoring the aripiprazole dosage in a patient cotreated with ritonavir-boosted PIs.

Pollack et al. [62] described two cases of quetiapine toxicity (increased sedation, worsened mental confusion, hyperglycaemia, weight gain) among patients with HIV with bipolar disorder concomitantly treated with atazanavir/ritonavir. This was potentially due to the inhibitory activity on CYP3A4, although a confirmatory PK analysis and/or quetiapine TDM were not performed. Similarly, Geraci et al. [63] reported a case of priapism in a patient with HIV affected by schizoaffective disorder treated with quetiapine and perphenazine concomitantly receiving lopinavir/ritonavir. The inhibitory activity of ritonavir on CYP3A4 and 2D6 may have increased antipsychotic agent concentrations potentially leading to prolonged α-adrenergic blockade and consequent low-flow priapism. According to the summary of product characteristics, quetiapine dose should be reduced by one-sixth in the case of co-administration with strong CYP3A4 inhibitors such as ritonavir, to prevent the occurrence of life-threatening adverse events (e.g. QT prolongation). Olanzapine should be considered as an alternative agent to replace quetiapine according to PK/PD properties in patients affected by COVID-19 treated with lopinavir/ritonavir [64].

Several case reports described the occurrence of life-threatening events associated with risperidone toxicity (serotonin syndrome, neuroleptic malignant syndrome, profound coma, extrapyramidal symptoms and late-onset angioedema) in patients with HIV treated with different ritonavir-boosted PIs [48, 65–68]. The underlying mechanism is probably due to inhibitory activity of ritonavir on CYP3A4 and CYP2D6, although in no cases was a PK analysis or TDM performed to prove risperidone overexposure. Notably, risperidone toxicity was also reported in a case of mild COVID-19 pneumonia requiring 14 days of lopinavir/ritonavir-based therapy [48].

Although the potential of DDIs of other antipsychotic agents with COVID-19 therapies has not been investigated in humans, clinically relevant interactions may be predicted according to the PK/PD properties of the different agents (Table 2 of the ESM). High-risk PK or PD interactions between antipsychotic agents (namely haloperidol, pimozide, sertindole, and ziprasidone) and antiretrovirals (darunavir/cobicistat or lopinavir/ritonavir) have been detected, mainly associated with an increase in antipsychotic exposure leading to life-threatening events (e.g. neuroleptic malignant syndrome, fatal arrhythmias caused by QT prolongation) [69, 70]. Consequently, coadministration should be cautiously avoided or antipsychotic dosage should be reduced (e.g. by one-sixth for quetiapine or 50% for iloperidone) [71]. Interestingly, a decrease in olanzapine exposure may occur during cotreatment with lopinavir/ritonavir, due to induction of CYP1A2 and UGT enzymes, possibly requiring an olanzapine dose increase [64]. The risk of PK or PD interactions between lopinavir/ritonavir and other antipsychotic agents may be moderate, and mainly concerns the risk of QT prolongation exhibited by each specific agent. Similarly, darunavir/cobicistat may increase the exposure of several antipsychotic agents metabolised by CYP3A4, thus requiring dose adjustments [69, 70]. According to CYP status, paliperidone and ziprasidone may be optimal alternatives to minimise the occurrence of clinically relevant interactions with PIs, although ziprasidone poses a high risk of QT prolongation in patients concomitantly treated with lopinavir/ritonavir.

In patients affected by a cytokine storm and treated with anti-IL-6 and/or anti-IL-1 agents such as tocilizumab, siltuximab and canakinumab, an upregulation of CYP3A4 activity may be expected [57]. Consequently, for those antipsychotic agents that are metabolised by CYP3A4, it might be necessary to increase the dosage to ensure efficacy, even if the magnitude of this increase is difficult to predict a priori. However, it should be mentioned that anti-IL-6 and IL-1 agents are used in patients with moderate-to-severe COVID-19 admitted to the ICU in which oral antipsychotic agents are usually stopped. Conversely, haloperidol is the only antipsychotic agent for which the magnitude of the effect could be clinically relevant in the ICU setting. When administered parenterally, a dosage increase could be needed to ensure adequate anti-delirium efficacy under these circumstances, closely monitoring QT prolongation and occurrence of torsade de pointes, regardless of potential drug interactions. Indeed, some patients may receive long-acting injectable antipsychotic agents to manage schizophrenia or bipolar disorder. In this scenario, clinically relevant drug interactions may also occur despite ICU admission because of the long elimination half-life of these agents.

Potential additive haematological toxicity should be considered when clozapine is used with tocilizumab, siltuximab, canakinumab and ruxolitinib. Additionally, higher clozapine concentrations could be detected in severe COVID-19 forms due to downregulation of CYP1A2 caused by pro-inflammatory cytokines, leading to potential life-threatening toxicity [21]. Notably, given that thioridazine is a moderate inducer of CYP3A4, a doubling of the daily dose of COVID-19

agents metabolised through this pathway should be consider (colchicine 1 mg × 2, ruxolitinib 10 mg × 2, or dexamethasone 12 mg instead of 6 mg).

No clinically relevant interactions involving remdesivir, enoxaparin, bamlanivimab and casirivimab/imdevimab are expected to occur with antipsychotic agents according to PK/PD properties. Overall, according to real-world evidence and PK/PD properties, lopinavir/ritonavir and darunavir/cobicistat pose the major concerns for the occurrence of clinically relevant interactions with antipsychotic agents. Higher exposure may occur for most of the first-generation and second-generation antipsychotic agents. Concomitant administration of PIs and haloperidol, quetiapine and pimozide should be avoided considering the significant increase in exposure. Ziprasidone and sertindole should be avoided according to the high risk of QT prolongation when concomitantly used with lopinavir/ritonavir. Haloperidol could be used in the ICU setting under strict monitoring. Olanzapine should be preferred as first-line therapy for the management of agitated delirium. Paliperidone could be used as a first-line alternative in severe psychosis according to its low risk of PK/PD interactions.

4.3 Mood Stabilisers

Clinically significant drug interactions between mood stabilisers and repurposed COVID-19 agents, especially with ritonavir-boosted PIs, were documented in healthy volunteers and in patients without COVID-19. Overall, two PK studies and eight case reports were identified by our search (Table 5).

Burger et al. [72] found a moderate reduction in lamotrigine exposure (32% in AUC) in 18 healthy volunteers concomitantly treated with atazanavir/ritonavir, due to an UGT induction. Similarly, van der Lee et al. [73] reported a significant decrease in lamotrigine disposition (50% in AUC and 46% in C_{max}) coupled with a 98% increase in drug CL among 18 healthy subjects concomitantly receiving lopinavir/ritonavir. Overall, the findings support the need for a lamotrigine dosage increase of 50–200% in patients cotreated with ritonavir-boosted PIs, and suggest that TDM may be a helpful tool in achieving adequate lamotrigine serum concentrations.

Several case reports described the occurrence of carbamazepine toxicity (e.g. vertigo, ataxia, drowsiness) in patients with HIV affected by epilepsy or seizure receiving ritonavir alone or in combination with lopinavir [74–78]. Therapeutic drug monitoring demonstrated a significant increase in carbamazepine serum concentrations, from 22 to 295%, due to inhibitory activity of ritonavir on CYP3A4. Coadministration of carbamazepine and ritonavir should be avoided or the carbamazepine dose should be reduced by at least 50% using a TDM-guided approach.

DiCenzo et al. [79] found a moderate increase in lopinavir exposure (respectively 1.75-fold and 1.33-fold in AUC and C_{max}) in eight patients with HIV concomitantly receiving valproate, while no significant variations in valproate disposition were caused by lopinavir/ritonavir. Conversely, Sheenan et al. [80] reported a significant decrease in valproate disposition in a patient with HIV affected by bipolar disorder concomitantly treated with lopinavir/ritonavir, responsible for the worsening of manic symptoms. Valproate serum concentrations were decreased by 48% (238 vs 495 µmol/L), possibly owing to the induction of UGT caused by lopinavir/ritonavir. Increase in valproate dosage may be needed in patients treated with ritonavir and PIs, and TDM is strongly suggested to assess the achievement of adequate valproate serum concentrations [80, 81]. A case report of serotonin syndrome in a patient affected by COVID-19 pneumonia treated with lopinavir/ritonavir and concomitantly receiving lithium and duloxetine was described [48], although unfortunately no PK analysis and/or TDM of lithium was performed.

A summary of predicted PK and PD interactions between mood stabilisers and other COVID-19 agents is shown in Table 3 of the ESM. Apart from the increased risk of thrombocytopenia in patients concomitantly treated with valproate and enoxaparin due to additive toxicity [82], and a potential electrolyte imbalance caused by dexamethasone that could impair lithium renal excretion (although the clinical relevance is questionable) [83], carbamazepine poses major issues when concomitantly used with several COVID-19 agents. The coadministration of carbamazepine with lopinavir/ritonavir or with darunavir/cobicistat should be avoided if not strictly necessary, or close monitoring of carbamazepine serum concentrations coupled with appropriate dose adjustments should be implemented. Given the strong inducer activity of carbamazepine on CYP3A4 [84], a significant reduction in the exposure of several substrates of this isozyme is expected, including remdesivir, colchicine, ruxolitinib and dexamethasone. An increased dosage of these agents should be considered.

In patients affected by a cytokine storm and treated with anti-IL-6 and/or anti-IL1 agents such as tocilizumab, siltuximab and canakinumab, an upregulation of CYP3A4 activity may be expected [57]. Consequently, as carbamazepine is metabolised by both CYP3A4 and CYP2C9/19, it might be necessary to increase its dosage to ensure efficacy, even if the magnitude of this increase is difficult to predict a priori. No clinically relevant interactions between other mood stabilisers and COVID-19 therapies (excluded lopinavir/ritonavir) are expected according to PK/PD properties of the different agents.

Overall, according to real-world evidence and PK/PD properties, carbamazepine poses the major concern for the occurrence of clinically relevant interactions with

COVID-19 agents, owing to strong induction of CYP3A4 activity. Furthermore, higher carbamazepine concentrations may occur in patients receiving lopinavir/ritonavir and/or darunavir/cobicistat, and coadministration should be avoided. If carbamazepine is strictly required (e.g. severe bipolar disorder in long-term therapy), dose adjustment (reduction by one-third) coupled with TDM should be performed. A double dose of lamotrigine or valproic acid is required in patients co-treated with lopinavir/ritonavir owing to induction of UGT activity.

4.4 Sedative Hypnotics

Clinically significant drug interactions between sedative hypnotics and COVID-19 agents, especially with ritonavir-boosted PIs, were documented in healthy volunteers and in patients without COVID-19. Overall, 11 PK studies mainly in healthy volunteers and one retrospective study were identified by our search (Table 6).

Villikka et al. [85] found a limited decrease in triazolam exposure (respectively 19% and 11% in AUC and C_{max}) in ten healthy volunteers concomitantly treated with dexamethasone. Furthermore, no differences in psychomotor tests were reported. No dose adjustments should be required for triazolam or other sedative hypnotics in patients cotreated with dexamethasone, given that its moderate inducer activity on CYP3A4 occurs at high doses (above 16–24 mg/day) [86].

Zhuang et al. [87] showed a significant decrease in midazolam exposure (respectively, 34% and 35% in C_{max} and AUC) after oral administration among 12 patients with arthritis with C-reactive protein levels above 8.0 mg/L who were cotreated with the anti-IL-6 agent sirukumab. The findings were due to a reversal of the inhibitory activity promoted by this proinflammatory cytokine on CYP3A4 isozyme. Consequently, an increase in midazolam dose could be necessary in patients with severe COVID-19 and an associated cytokine storm when concomitant treatment with anti-IL-6 (i.e. tocilizumab, siltuximab), to achieve adequate sedation. The magnitude of this increase is difficult to predict a priori according to the different midazolam formulations (oral vs parenteral) and degree of disease severity (IL-6 levels) [88].

Mathias et al. [89] found a significant increase in midazolam exposure (respectively, up to 3.9-fold and 19-fold for C_{max} and AUC) coupled with a relevant decrease in CL (up to 20.1-fold) among 72 healthy volunteers treated with cobicistat, owing to strong inhibitory activity on CYP3A4. Coadministration of midazolam and a strong inhibitor of CYP3A4 should be avoided, or intravenous administration of midazolam with cobicistat should be only considered in the ICU setting where close monitoring of respiratory function should be performed [69].

Several PK studies investigated the impact of ritonavir and/or of ritonavir-boosted PIs on benzodiazepine metabolism and exposure [90–95]. Greenblatt et al. [90] found a significant increase in alprazolam exposure (2.48-fold in AUC) in ten healthy volunteers concomitantly receiving ritonavir, leading to augmented sedation and performance impairment. Similarly, Menon et al. [91] found a moderate increase in alprazolam disposition (34% in AUC) in 12 healthy subjects receiving paritaprevir/ritonavir, due to inhibitory activity of ritonavir on CYP3A4. In the same study [91], authors also reported no significant variations in zolpidem exposure in 12 healthy volunteers with concomitant administration of paritaprevir/ritonavir. A significant increase in midazolam exposure (respectively from 3.02-fold to 26.41-fold for AUC and from 1.15-fold to 4.27-fold for C_{max}) in healthy volunteers concomitantly treated with ritonavir alone or ritonavir-boosted PIs has been reported, caused by strong inhibition of CYP3A4 [92–95]. Notably, a more pronounced increase in midazolam disposition was found with oral compared with intravenous administration [95]. The concomitant use of midazolam and ritonavir should be avoided, or solely reserved for intubated ICU patients in which lower midazolam dosage should be required to achieve adequate sedation [69]. A retrospective cohort study [96] including 241 patients with HIV undergoing bronchoscopy reported an increased relative risk of severe prolonged sedation (risk ratio (RR) 6.21; 95% confidence interval 1.53–25.12) in patients receiving intravenous midazolam (median dose 4 mg) concomitantly treated with ritonavir-boosted PIs compared with those using other antiretroviral agents. Greenblatt et al. [97] found a significant increase in triazolam exposure (20.39-fold in AUC) in six healthy volunteers receiving ritonavir, due to strong inhibitory activity on CYP3A4 and resulting in increased sedation and impairment of psychomotor performance. Similarly, Culm-Merdeck et al. [98] reported a relevant increase in triazolam disposition (21.1-fold in AUC) in 23 healthy subjects concomitantly treated with ritonavir. Consequently, coadministration of triazolam and ritonavir-boosted PIs should be avoided to prevent excessive sedation and respiratory depression. Conversely, ritonavir caused only a moderate increase in zolpidem exposure (respectively 1.28-fold and 1.22-fold in AUC and C_{max}) [97], thus

A summary of predicted PK and PD interactions between sedative hypnotics and COVID-19 agents is shown in Table 4 of the ESM. A high or moderate risk of clinically relevant drug interactions may be expected only when sedative hypnotics that are substrates of CYP3A4 are concomitantly used in patients with COVID-19 receiving antiretroviral agents that are strong CYP3A4 inhibitors, namely ritonavir or cobicistat. The combination may potentially cause severe prolonged sedation associated with respiratory depression (particularly with midazolam and triazolam). In

this scenario, the use of oxazepam-like benzodiazepines (namely lorazepam, lormetazepam, oxazepam and temazepam), exhibiting no metabolism through CYP450 pathway, should be preferred [99]. According to the study of Zhuang et al. [87], a higher midazolam dose could be required to provide adequate sedation in patients with severe COVID-19 affected by a cytokine storm and managed with anti-IL-6 agents (tocilizumab or siltuximab).No clinically relevant interactions involving remdesivir, colchicine, dexamethasone, enoxaparin, ruxolitinib, bamlanivimab and casirivimab/imdevimab are expected to occur with sedative hypnotics according to PK/PD properties.

Overall, according to real-world evidence and PK/PD properties, sedative hypnotics metabolised by CYP3A4 pose the major concern for the occurrence of clinically relevant interactions with lopinavir/ritonavir and darunavir/cobicistat. Concomitant administration of midazolam and triazolam with PIs should be avoided in non-ICU patients. Oxazepam-like benzodiazepines (i.e. lorazepam, lormetazepam, oxazepam and temazepam) should be preferred as first-line therapy for the management of anxiety disorders by virtue of a favourable PK/PD profile.

5 Conclusions and Perspectives

Overall, real-life experiences of clinically relevant drug interactions between psychotropic medications and repurposed COVID-19 agents occurring in patients with severe acute respiratory syndrome coronavirus 2 infection are scarce. Only two case reports describing the onset of serotonin syndrome in patients with COVID-19 cotreated with lopinavir/ritonavir and duloxetine, risperidone or lithium exist [48]. Unfortunately, no PK analysis or TDM was performed in these cases to prove the increased exposure of psychotropic agents resulting from inhibitory activity on CYP450 exhibited by ritonavir.

The PK studies that investigated the impact of repurposed COVID-19 agents on psychotropic medications in the majority of cases were performed among healthy subjects (Tables 3, 4, 5, 6). Accordingly, translation of these findings to patients with severe COVID-19 may be questionable, considering that the magnitude of the impact of DDIs due to multi-organ failure and/or to cytokine storm often occurring in patients with COVID-19 could not be adequately addressed [12]. Nevertheless, the available studies provide essential findings to prioritise the risk of clinically relevant drug interactions in patients with COVID-19, calling for avoidance of certain associations (e.g. midazolam/triazolam with lopinavir/ritonavir [92–95, 97, 98]), for some dose adjustments (e.g. lamotrigine or carbamazepine when lopinavir/ritonavir is used [72–79]) or for some psychotropic

replacement (e.g. olanzapine instead of quetiapine in case of concomitant use of lopinavir/ritonavir or darunavir/cobicistat [58, 59]).

According to PK/PD properties and available evidence, antiretrovirals containing strong inhibitors of CYP450 (lopinavir/ritonavir and darunavir/cobicistat) pose the major issues in terms of potential occurrence of clinically relevant drug interactions with several antipsychotic agents. This represents an important concern given that lopinavir/ritonavir and darunavir/cobicistat were used in mild-to-moderate forms of COVID-19 (also including outpatient management), in which long-term concomitant treatment with oral psychotropic agents are usually maintained. In contrast, in patients with severe COVID-19 requiring ICU admission, long-term therapies (including psychotropic agents) are abruptly suspended, and thus the risk should be lower in this setting. In this latter scenario, only a few drugs are commonly used through parenteral administration to provide adequate sedation or a delirolytic effect (e.g. midazolam, haloperidol), and potential relevant drug interactions could be successfully managed thanks to the fact that ICU patients are intubated (i.e. no risk of severe respiratory depression caused by midazolam overexposure) and carefully monitored (i.e. early identification of QT prolongation caused by increased disposition of haloperidol). Indeed, some patients may receive long-acting injectable antipsychotic agents to manage schizophrenia or bipolar disorder. In this scenario, clinically relevant drug interactions may also occur despite ICU admission because of the long elimination half-life of these agents.

Notably, the use of lopinavir/ritonavir and darunavir/cobicistat in COVID-19 is currently limited, owing to poor evidence of efficacy in severe acute respiratory syndrome coronavirus 2 infection [100, 101], and this decreases considerably the risk of clinically significant interactions. A practical algorithm to manage the occurrence of clinically relevant drug interactions between psychotropic medications and COVID-19 agents according to disease severity is provided in Fig. 2. In outpatient/inpatient scenarios concerning mild-to-moderate COVID-19, antiretrovirals (lopinavir/ritonavir and darunavir/cobicistat) represent the agents showing the higher risk of significant drug interactions. While in the case of concomitant administration with antidepressants, only a moderate risk of clinically relevant interactions could be recognised according to an increase in antidepressant exposure and QT prolongation (e.g. citalopram, fluoxetine, TCAs, trazodone), a high risk of significant interactions resulting in life-threatening events could be expected with several antipsychotic agents (i.e. haloperidol, quetiapine), mood stabilisers (i.e. carbamazepine) and sedative hypnotics (i.e., midazolam, triazolam). Notably, the dosage of different psychotropic agents (e.g. bupropion, olanzapine, lamotrigine) should be increased in the case of concomitant

administration with antiretrovirals to achieve desired effects. In this scenario, the use of psychotropic agents (e.g. oxazepam-like benzodiazepines, olanzapine), exhibiting no or minimal metabolism through the CYP450 pathway (particularly CYP3A4), should be preferred. Conversely, in inpatient/ICU scenarios concerning moderate-to-severe COVID-19, no concerns for the occurrence of clinically relevant interactions with psychotropic agents exist, given that oral medications are usually abruptly suspended. Anti-inflammatory therapies used for severe COVID-19 pose no relevant PK/PD issues able to cause high-risk drug interactions with psychotropic agents. Only the use of anti-IL-1 or IL-6 agents may reverse the inhibitory effect of pro-inflammatory cytokines on CYP450, thus potentially causing underexposure of midazolam or haloperidol, while carbamazepine may reduce the disposition of different COVID-19 therapies (e.g. colchicine, dexamethasone, ruxolitinib).

Interestingly, Anmella et al. [102] provided practical recommendations for patients affected by psychiatric disorders requiring concomitant treatment with lopinavir/ritonavir in the COVID-19 setting. Electrocardiogram monitoring was recommended for properly managing expected PK/PD interactions, leading to QT prolongation and potential life-threatening arrhythmias. Additionally, three different clinical scenarios were discussed. First, olanzapine was recommended as first-line therapy in agitated delirium, and quetiapine should be avoided. This is consistent with the findings reported in PK studies and in case reports [58, 59, 62–64, 71]. Second, essential treatments (e.g. antipsychotic agents, mood stabilisers) should be maintained in severe mental illness and should be prioritised, avoiding abrupt withdrawal. In this scenario, careful monitoring for clinically relevant PK/PD interactions coupled with dose adjustment should be implemented. This is especially true when psychotropic agents at high risk for drug interactions are co-administered with lopinavir/ritonavir. Third, in non-severe mental illness with depressive/anxiety symptoms, psychological support coupled with prompt identification and treatment of symptoms should be provided. In this scenario, the use of antidepressants or sedative hypnotics showing a low risk for PK/PD interactions with COVID-19 agents (e.g. oxazepam-like benzodiazepines, fluoxetine, sertraline) should be preferred. This is consistent with the findings reported in PK studies [44, 45]. It should not be
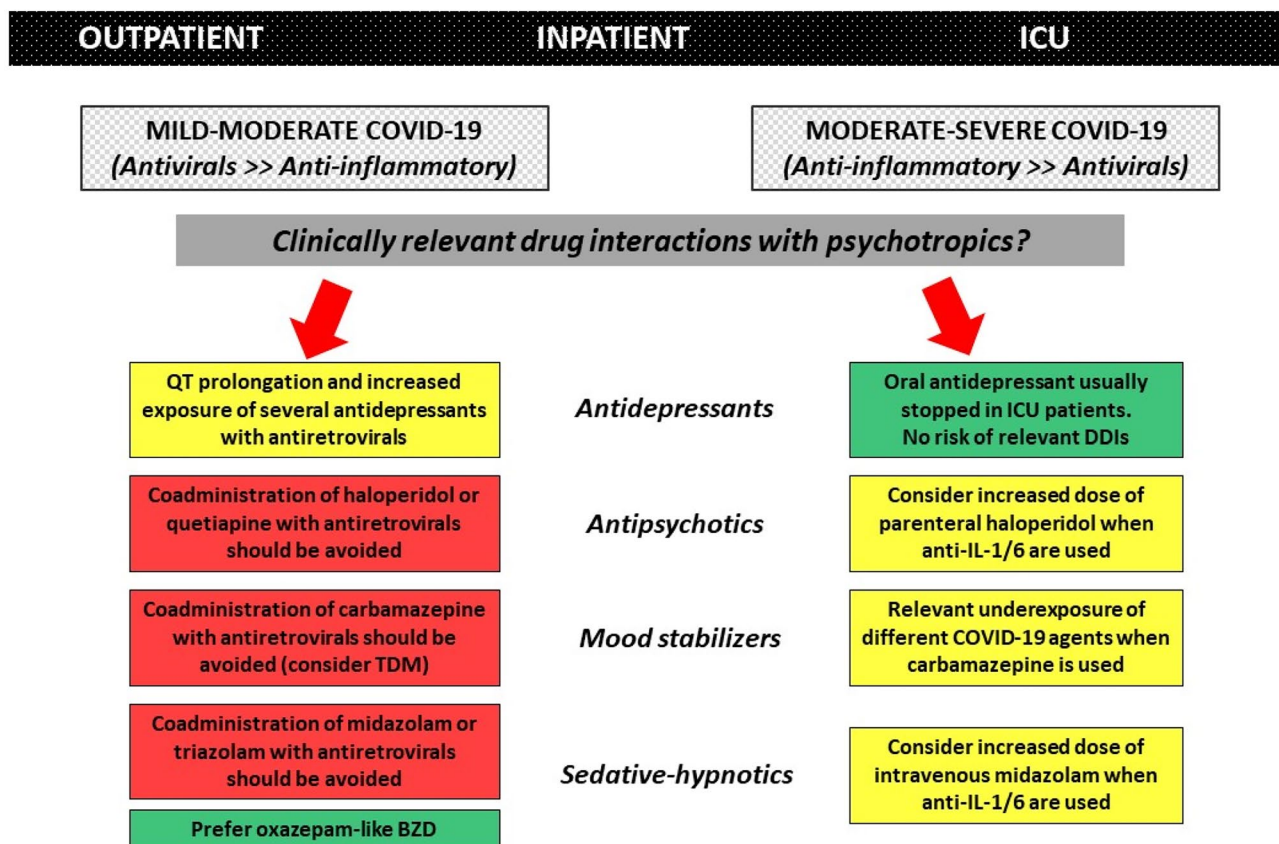

Fig. 2 Proposed algorithm for the management of potential clinically relevant interactions between psychotropic medications and repurposed COVID-19 agents according to disease severity/stage of the infection. *BZD* benzodiazepine, *DDIs* drug–drug interactions, *ICU* intensive care unit, *IL* interleukin, *TDM* therapeutic drug monitoring

overlooked that close monitoring should be performed whenever dose adjustments are extended beyond the recommendations provided in the summary of product characteristics of a specific agent. Furthermore, in the case of PD interactions leading to QT prolongation or other additive toxicity (e.g. hepatic, haematological), tailored monitoring should be promptly implemented.

Notably, the potential interaction profile of remdesivir is not fully understood, given that only in vitro evidence with unclear clinical implications is available, and no in vivo drug interaction study has been performed or cases of relevant interactions described [103]. In vitro studies demonstrated that remdesivir could exhibit moderate or weak inhibitory activity respectively on CYP3A4 or CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isozymes, and a relevant inhibitory effect on carboxylesterase-2 through covalent modifications has been reported [103, 104]. However, the clinical relevance of these findings is questionable considering that remdesivir is a pro-drug that is rapidly degraded in vivo, and therefore the potential for clinically significant drug interactions is likely to be limited. Administration of sedative hypnotics that are substrates of CYP3A4 2 hours after a remdesivir infusion has been recommended to avoid potentially relevant interactions in the case of cotreatment [29].

In conclusion, clinically relevant drug interactions between psychotropic medications and COVID-19 agents mainly concern antiretrovirals. The poor efficacy showed by lopinavir/ritonavir and/or darunavir/cobicistat in COVID-19 prospective clinical trials to date has led to a decrease in their use. Therefore, the risk of occurrence of relevant interactions is currently quite limited. The major issue that is still to be addressed is represented by the impact that a DDI may have on psychotropic agents in patients with moderate-to-severe COVID-19. Multi-organ failure and a cytokine storm occurring in the late stage of COVID-19 infections might be responsible of high-risk DDIs with psychotropic medications whose magnitude and clinical relevance unfortunately are still to be defined.

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Declarations

Conflict of interest Federico Pea participated in the speaker bureau for Angelini, Basilea Pharmaceutica Gilead, Hikma, Merck Sharp and Dohme, Nordic Pharma, Pfizer and Sanofi Aventis, and in an advisory board for Angelini, Basilea Pharmaceutica, Correvio, Gilead, Merck Sharp and Dohme, Nordic Pharma, Novartis, Pfizer and Thermo–Fisher. Milo Gatti and Fabrizio De Ponti have no conflicts of interest that are directly relevant to the content of this article.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

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Author contributions MG and FP made substantial contributions to the conception of the manuscript. MG was involved in drafting the manuscript. FDP and FP made substantial contributions in critically revising the manuscript for important intellectual content. All the authors approved the final version of the manuscript.

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