Drug interactions associated with psychotropic medication and COVID-19

**Valentin Oprea, Nicolae Bacinski,
Anastasia Caracas**

Valentin Oprea - MD Ph.D. Associate professor, Chair of psychiatry, narcology and medical psychology, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chișinău, Republic of Moldova

Nicolae Bacinski - MD Ph.D. Professor, Department of Pharmacology and Clinical Pharmacology, "Nicolae Testemițanu" State University of Medicine and Pharmacy Chișinău, Republic of Moldova

Anastasia Caracas - Resident, Department of Pharmacology and Clinical Pharmacology, "Nicolae Testemițanu" State University of Medicine and Pharmacy Chișinău, Republic of Moldova

ABSTRACT

SARS CoV-2 infection or COVID-19 disease has triggered a global pandemic and requires a complex approach, given the multisystemic impairment and lack of specific etiological treatment. The diversity of drug groups, used for non-specific, pathogenetic, and symptomatic treatment, may expose the patient to a significant risk of developing drug interactions. The long-term treatment of a psychiatric patient may predispose to an increased risk for side effects, especially in the association of chronic somatic pathologies that require the administration of specific preparations. Psychotropic drugs are associated with adverse effects on the cardiovascular system (cardiotoxicity, QT prolongation), central nervous system (convulsions), and hematopoietic system (neutropenia, agranulocytosis, lymphopenia), which may overlap with concomitant use with other groups of drugs. Drug interactions in these cases may have an increased incidence with unpredictable manifestations. The elucidation of the mechanisms underlying drug interactions and the possibility of anticipating the occurrence of clinically relevant interactions is extremely important for clinicians.

KEYWORDS

Drug interactions, psychotropic medication, SARS CoV-2, COVID-19, side effects.

INTRODUCTION

The SARS CoV-2 pandemic has led to a reorganization in the health system, an extraordinary mobilization of scientific research in many areas of medicine to develop specific drugs (antivirals, vaccines, etc.), and anti-epidemic measures. At the same time, the coronavirus revealed a series of pathological changes from organs and systems that required a review of treatment tactics, including in psychiatry, of patients with those pathologies infected with SARS CoV-2. In this context, the number of groups and preparations used simultaneously increased significantly, which further raised the issue of drug interactions (1).

People with mental disorders are more vulnerable to the novel coronavirus COVID-19 than the general population due to the risk of infection (including pneumonia), barriers to timely access to healthcare facilities because of their isolation in the psychiatric ward, and the fear, anxiety and depression accompanying the pandemic process. The long-term side effects of psychotropic drugs (metabolic syndrome, extrapyramidal symptoms, electrolyte imbalance, etc.), physical health problems (obesity, gynecomastia, sexual dysfunction, etc.), substance use disorders (nicotine, alcohol, marijuana, etc.), and medication non-adherence are other important problems in the fight against COVID-19. Risky combinations and drug–drug interactions (DDIs) occur as a

result of COVID-19 treatment concomitant with psychotropic drugs, which are indispensable in chronic mental disorders (2). Preparations with fixed combinations, along with drug combinations, are increasingly used in the treatment of many diseases and represent an important risk factor for the occurrence of drug interactions, including clinically relevant changes in the efficacy or safety of a drug therapy (3). Drug interactions can occur on a pharmacokinetic level (absorption, distribution, metabolism, elimination) and pharmacodynamic level (receptors, tissues, organs, systems) with synergistic or antagonistic consequences, sometimes unpredictable (4).

Psychotropic preparations (antipsychotics, anxiolytics, antidepressants, antiepileptics, psychostimulants, thymoleptics, etc.) may interact with the drugs metabolized by hepatic cytochrome P450 isoenzymes (CYP 2D6, 2C9, 2C19, and 3C19), and with their inducers or suppressors. Drug interactions that can occur during concomitant use of psychotropics with other drugs with similar properties may cause a rise in serious adverse reactions, lack of efficacy, or clinically significant tolerability issues. The clinical relevance of many drug interactions is slightly underestimated because detection is difficult and possible outcomes can vary widely (5) (fig.1).

Figure 1. Effects of CYP450 inducers and inhibitors on CYP450-metabolized drug substrates (6)

DRUG INTERACTIONS

It is necessary to analyze and specify the drug interactions that may occur when using drugs for the treatment of COVID-19 and psychotropic drugs, widely used in psychiatric practice. Elucidation of the mechanisms of pharmacokinetic and pharmacodynamic interactions may be essential to prevent the occurrence of relevant drug interactions and to optimize therapy in patients with psychiatric pathology and COVID-19.

Azithromycin

Azithromycin does not interact significantly with the hepatic cytochrome P450 system and it does not produce its induction or inhibition due to which pharmacokinetic drug interactions are not relevant. Azithromycin is known to be a P-glycoprotein (P-gp) inhibitor and, in case of co-administration with P-gp substrates (e.g. digoxin, colchicine), it has been reported to result in increased serum levels, requiring monitoring. Psychotropics are not known to be P-gp substrates, and do not interact with azithromycin at this level (7, 8).

Pharmacodynamic interactions were found due to QT prolongation, when azithromycin was co-administered with psychotropics, a characteristic effect of macrolide, antipsychotics and antidepressants, which require careful use and/or electrocardiogram monitoring. Azithromycin presents a major risk for QT prolongation when is combined with citalopram, escitalopram, amisulpride, ziprasidone, clozapine, pimozide, haloperidol and thioridazine, and a moderate risk when is combined with amitriptyline, clomipramine, trazodone, imipramine, aripiprazole, chlorpromazine, olanzapine, paliperidone, perphenazine, quetiapine, risperidone and lithium. Also, it is necessary to take into account the side effects of azithromycin, such

as catatonia, delirium, agitation, anxiety, psychotic depression, and drowsiness, when combined azithromycin with psychotropics. A potential adverse effect of azithromycin is myelosuppression, and some psychotropic drugs may cause also neutropenia or agranulocytosis (especially clozapine and carbamazepine), with an increased risk of inhibiting hematopoiesis (7, 8, 9).

Cloroquine and hidroxicloroquine

Both preparations, due to the prolongation of the QT interval and their torsadogenic potential, have an increased risk of interactions with psychotropic drugs. Despite not being formerly contraindicated, co-administration of hydroxychloroquine and the drugs that prolong the QT interval is not recommended (10).

CYP enzymes (CYP2C8, CYP3A4, CYP2D6 and CYP1A1) catalyze the dealkylation of chloroquine and hydroxychloroquine to pharmacologically active metabolites. The combination of chloroquine and hydroxychloroquine with psychotropic drugs that inhibit CYP3A4 may cause side effects due to elevated levels of antimalarial drugs. CYP3A4 inducers (carbamazepine, oxcarbazepine) may lower chloroquine or hydroxychloroquine levels. Hydroxychloroquine is an inhibitor of CYP2D6. Several psychotropic drugs (fluoxetine and paroxetine) are potent inhibitors of CYP2D6 and may increase hydroxychloroquine levels. In turn, HCQ can inhibit CYP2D6 and increase the levels of aripiprazole, atomoxetine, paroxetine, risperidone, venlafaxine, vortioxetine and several tricyclic antidepressants. Cardiac side effects of chloroquine and hydroxychloroquine (QT prolongation, atrio-ventricular block) should be monitored when are prescribed in combination with psychotropic drugs that prolong the QT

interval. In addition, clinicians will need to be vigilant for the emergence of drug induced psychosis. Chloroquine may antagonize the antiepileptic effect of carbamazepine (9, 11, 12).

Chloroquine and hydroxychloroquine have not been shown interactions with lamotrigine, valproic acid and clonazepam. Hydroxychloroquine may reduce the seizure threshold, and when combined with some antipsychotics (clozapine, chlorpromazine, risperidone, bupropion, etc.) and antidepressants (clomipramine, maprotiline, etc.) may increase the risk of seizures. It should be noted that a history of seizures, CNS damage, metabolic disturbances, concurrent use of other drugs that lower the seizure threshold and drug metabolism may increase the probability that an antipsychotic drug may induce seizures (13, 14).

Sertraline is metabolised by CYP2D6, CYP3A4, CYP2B6, CYP2C9, CYP2C19 and inhibits CYP2D6 with less potency than fluoxetine and paroxetine. Sertraline may increase the risk of hypoglycaemia when is co-administered with chloroquine and hydroxychloroquine (15).

Citalopram increases the QT interval in a dose-dependent manner, and may precipitate the occurrence of torsade de pointes. A European decision has contraindicated the use of citalopram (and its isomer escitalopram) with any other potentially torsadogenic drugs, including hydroxychloroquine. However, this is easily manageable in the context of COVID-19. Indeed, as the maximum recommended duration of hydroxychloroquine treatment is 10 days, the interruption of citalopram or escitalopram for such a short period should not expose the patient to the risk of recurrence of depression. Switching to another serotonin reuptake

inhibitor (SSRI) is possible, as the pharmacodynamic effect immediately replaces that of the preceding SSRI, even if the pharmacokinetic equilibrium of the new antidepressant may take some time (10).

The combination of chloroquine and hydroxychloroquine with lithium preparations, antidepressants (amitriptyline, clomipramine, citalopram, escitalopram, trazodone), antipsychotics (chlorpromazine, clozapine, haloperidol, pimozide, quetiapine, zuclopenthixol, ziprasidone) and anxiolytics (hydroxyzine) require medical attention due to prolongation of QT interval. Antidepressants (sertraline, reboxetine, milnacipran, agomelatine, bupropion) and antipsychotics (aripiprazole, amisulpride, asenapine, olanzapine, paliperidone, perphenazine) have lower side effects and fewer interactions with hydroxychloroquine and chloroquine (9).

Famotidine

Famotidine is considered a weak CYP1A2 inhibitor and may lead to substantial increases in blood concentrations of CYP1A2 substrates. Whilst there are no reports, theoretically, co-administration can lead to increased levels of clozapine, olanzapine and agomelatine as they are predominantly CYP 1A2 substrates. Famotidine may cause QTc prolongation. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. In general, the risk of an individual agent, or a combination of these agents, causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease and electrolyte disturbances. In addition, the extent of drug-

induced QT prolongation is dependent on the particular drug involved and dosage of the drug (7).

Lopinavir / ritonavir

Lopinavir is metabolized extensively by the hepatic cytochrome P450 system, almost exclusively by CYP3A. Ritonavir is also noted to be extensively metabolized by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Ritonavir is a potent CYP3A and CYP2D6 inhibitor, and is given with lopinavir to increase plasma levels of lopinavir. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19, thereby increasing the biotransformation of some drugs metabolized by these pathways. This may result in decreased systemic exposure of these agents and therapeutic failure (7, 16).

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is metabolized by N-demethylation, mediated by CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Fluoxetine and its active metabolite (norfluoxetine) markedly inhibit CYP2D6, moderate CYP2C9, weak to moderate CYP2C19 and CYP3A4, and weak CYP1A2 increase the Area Under The Curve (AUC) of the ritonavir without significant changes in other pharmacokinetic parameters.

This relatively low drug-drug interaction does not need dosage adjustment. On the other hand, there is a possibility of serotonin syndrome in concomitant use of ritonavir with SSRIs (15).

Serotonin syndrome is one of the important adverse drug reaction (ADRs) associated with the use of drugs affecting serotonin reuptake, caused by excessive activation of postsynaptic serotonin receptors. In one study, the incidence of this adverse reaction in ICU was

estimated to be 39%. This syndrome can occur due to overdose with single serotonin agents, but most of the severe cases are because of interaction between two or more drugs increasing serotonin transmission. (17) Citalopram and escitalopram are metabolized by CYP3A4, CYP2C19, and CYP2D6. They both have a weak inhibitory effect on CYP2D6, so it does not appear to cause significant changes in ritonavir levels. Ritonavir inhibits CYP 3A4 but the interaction with these antidepressants is not clinically significant (15).

Quetiapine is a CYP3A4 substrate and concomitant treatment with ritonavir and other protease inhibitors can increase its serum concentrations. For this reason, FDA recommends reducing the dosage of quetiapine to 1/6th and to monitor for quetiapine related adverse effects. Combination of the oral solution of Ritonavir / Lopinavir, which contains 42.4% ethanol alcohol, with disulfiram may trigger reactions characteristic for acetaldehyde dehydrogenase inhibitor. Ritonavir/Lopinavir may exacerbate metabolic adverse reactions, also caused by second-generation antipsychotics, but this is not of great significance as COVID-19 approved drugs are given only for short term (3, 18).

A clinically significant drug interaction may occur when risperidone is co-administered with protease inhibitors. A number of case reports have documented the occurrence of ADRs such as extrapyramidal symptoms, reversible coma, neuroleptic malignant syndrome, and late-onset angioedema in patients receiving risperidone associated with ritonavir/indinavir, presumably due to inhibition of risperidone metabolism (3).

Severe infections are usually manifested with signs of generalized inflammation including

fever and serum C-reactive protein (CRP) elevations secondary to the cytokines released that can inhibit several CYPs. Inflammation can increase serum clozapine concentrations. More limited is the information on olanzapine, which is also metabolized by CYP1A2, and on the antipsychotics CYP3A4 metabolized. This specific DI, caused by inflammation-released cytokines, may be relevant for clozapine use, because of the narrowest therapeutic index of all atypical antipsychotics. This may explain why in a study of the ADRs reported to the FDA, clozapine ranked as the third most lethal drug with 3277 deaths. Decreasing the clozapine dosage during infections with systemic inflammation may be necessary. Cases of clozapine intoxication are starting to be described during pneumonia associated with the COVID-19 disease (3).

In patients with symptoms of COVID-19, they suggested rapid antigen testing as well as complete blood count testing, to distinguish COVID-19-related symptoms from side-effects of clozapine. They recommended continuation of clozapine in patients with COVID-19 infection, and only dose adjusting if necessary, preferably as guided by plasma levels of clozapine. Another recommendation was to initiate vitamin D supplementation in all patients taking clozapine, considering the high rates of low vitamin D in patients with schizophrenia and some possible protective effects in decreasing the likelihood of COVID-19 respiratory infection (19).

The use of lopinavir/ritonavir is contraindicated with medications that include pimozide, midazolam, and triazolam due to increased drug levels and potentiation of adverse effects. Therefore, is recommended to use benzodiazepines not metabolized by CYP enzymes (lorazepam, temazepam, or oxazepam). Owing to CYP450 enzyme or

glucuronidation-inducing effects, ritonavir-boosted protease inhibitors also have been shown to lower concentrations of some psychotropics (e.g., bupropion, methadone, lamotrigine, and olanzapine), thus leading to increased dose requirements of these medications. Other potential nonpsychiatric side effects that may have implications for psychiatrists include Stevens Johnson syndrome, diabetes mellitus, QTc prolongation, pancreatitis, neutropenia, hepatotoxicity, and chronic kidney disease (8, 9).

Tocilizumab

Tocilizumab has no direct inducing or inhibitory effects on cytochrome P-450 enzymes. Increased IL-6 during the cytokine storm inhibits the activity of CYP3A4, CYP2C19, CYP2C9 and CYP1A2 with reduced metabolism and increased exposure to their substrate drugs. The preparation, by removing IL-6-induced suppression of cytochrome P-450, will require dose adjustment (16, 20).

Caution should be exercised when tocilizumab is co-administered with myelotoxic medicinal preparations such as clozapine or carbamazepine due to the potential additive effect on hematological toxicity. No clinically significant effect was found on the QT interval in healthy subjects (12).

Tocilizumab might cause vascular disorders (hypertension), and nervous system disorders (headache, demyelinating disorders, leukoencephalopathy with cognitive impairment, and peripheral neuropathy). A serious adverse effect reported with tocilizumab is increasing the risk of fungal and bacterial infections which should be considered in COVID-19 patients (20).

Antipsychotics have been associated with immunosuppressive properties, such as decreased pro-inflammatory cytokine levels, blood dyscrasias, and altered production of antibodies. The risk of neutropenia is about 1% for clozapine (3% in the elderly) and 0.1% for phenothiazines, while for other medications data are limited. Furthermore, both first- and second-generation antipsychotics have been associated with a higher risk of pneumonia in observational studies. Data from randomized trials

including mostly second-generation antipsychotics showed a higher risk of infections. Apart from immunity abnormalities, multiple mechanisms may contribute, including reduced clearance of the airways (related to central sedation and inhibition of cough), impaired chest movements and swallowing due to extrapyramidal symptoms, and sialorrhea (1).

CONCLUSIONS

1. Drug interactions associated with the administration of psychotropic drugs and reprofiled drugs for Covid 19 are on pharmacokinetic and pharmacodynamic level.
2. QT prolongation is a clinically relevant adverse event, characteristic for psychotropic drugs and drugs for Covid 19 (azithromycin, chloroquine, hydroxychloroquine, famotidine, etc.), which require monitoring due to possible cardiovascular complications.
3. Immune disorders during SARS-CoV-2 infection may promote the development of psychotropic (neuroleptic) side effects, such as the risk of developing infections, myelosuppression.
4. Cytochrome P450 microsomal enzymes inhibition and/or induction of concomitantly administered drugs cause important pharmacokinetic interactions. Increasing the concentration of the drug may induce the development of toxicity, and decreasing the concentration reduces the therapeutic effect of the drug. Comprehension of metabolic pathways and possible drug interactions would allow the anticipation of unwanted complications.
5. Overlapping of side effects of drugs used in Covid 19 and symptoms of psychiatric pathology are a problem in clinical practice and require rigorous monitoring.

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Correspondence:

Valentin Oprea,

MD Ph.D. Associate professor, Chair of psychiatry, narcology and medical psychology, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chișinău, Republic of Moldova,
valentin.oprea@usmf.md

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