https://doi.org/10.31925/farmacia.2022.3.2 **REVIEW**

CHALLENGES REGARDING THE INTERACTION BETWEEN PSYCHOTROPICS AND COVID-19 CO-MEDICATION

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Abstract

Coronavirus disease 19 (COVID-19) pandemic is at the moment the main topic of interest regarding medical science and research. Responsible for the disease is a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) accountable for over 118 million cases and a total of 2.61 million deaths worldwide (July 2020). Drug treatment for infected COVID-19 patients represents a difficult task, since there is no currently licensed specific antiviral for SARS-CoVs, the clinical approach of these patients remains the symptomatic one and also providing supportive care if needed. The clinical approach becomes more of a challenge especially if one has a co-existing psychiatric illness under psychotropic treatment. This concern is raised due to potential drug-to-drug interactions (DDIs) between antiviral agents and psychotropics, not only by common metabolic pathways regarding P450 cytocromial enzymes but also by pharmacological synergism regarding common adverse effects. Thus, we searched to identify studies published in PubMed medical database to support clinical practice in these situations and found that mostly all main psychotropics are implied in DDIs with the antivirals used to treat COVID-19 infection. Therefore, the clinical approach in treating COVID-19 patients with antiviral agents remains a challenge especially for those who have a comorbid psychiatric illness and are under treatment with psychotropics.

Rezumat

Pandemia COVID-19 este în momentul de față principalul subiect de interes al științei și cercetării medicale. Responsabil pentru această patologie este noul coronavirus, virusul SARS-CoV-2, responsabil pentru un număr total de 118 milioane de infecții la nivel global, dintre care 2,61 milioane de decese (iulie 2020). Managementul terapeutic al infecției COVID-19 reprezintă o provocare ținând cont că până în momentul de față nu există tratament curativ antiviral pentru SARS-CoV-2, astfel abordarea terapeutică pentru acești pacienți vizează simptomatologia și suportul vital unde este necesar. Abordarea terapeutică este cu atât mai dificilă în cazul pacienților care prezintă o patologie psihiatrică comorbidă pentru care urmează tratament psihotrop, nu numai din cauza multiplelor interacțiuni medicamentoase cu privire la calea comună de metabolizare la nivelul enzimelor citocromului P450, ci și din cauza efectelor adverse apărute prin sinergism farmacologic. Au fost căutate studii publicate în baza de date PubMed pe această tematică, concluzia fiind că majoritatea psihotropelor sunt implicate în interacțiuni medicamentoase cu agenții antivirali utilizați pentru infecția SARS-CoV-2. Prin urmare, abordarea terapeutică în tratamentul infecției COVID-19 rămâne o provocare în cazul pacienților care prezintă comorbidități psihiatrice aflate sub tratament psihotrop.

Keywords: COVID-19, antivirals, psychotropics, interaction

Introduction

The initial disease outbreak was described in Wuhan City, Hubei Province, China on 12 December 2019. The World Health Organization (WHO) announced the official designation for the current CoV-associated disease to be COVID-19, caused by SARS-CoV-2 on 11 February 2020. A similar disease was described in 2002 as severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1), being responsible for over 8000 cases and at least 774 deaths worldwide. Coronaviruses (CoVs) belong to the *Coronaviridae* family, consisting of seven members that infect humans, including human CoV 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and now SARS-CoV-2, viruses producing symptoms and diseases ranging from the common cold to severe fatal illnesses such as SARS or Middle East respiratory syndrome (MERS). Phylogenetic studies have revealed that SARS-CoV-2 has 88% similarity to two SARS-like CoVs derived from bat SARS-like CoVs (bat-SL-CoVZC45 and bat-SL-CoVZXC21). Like other CoVs, it possesses an unsegmented, single-stranded, positive-sense RNA genome of around 30kb. Molecular studies have revealed an overall 80% nucleotide identity between SARS-CoV-2 and SARS-CoV, and 89% identity with the bat SARS-like CoVs ZC45 and ZXC21. Regarding treatment options of an infected patient, to date, there is no specific antiviral agent. However, many antivirals and immunomodulators are used to treat the infection, among which the most frequently used being hydroxychloroquine (HCLQ),

ritonavir in association with lopinavir (LPV/r), favipiravir (FAVI) and remdesivir (RDV) [1]. The clinical approach of patients treated with these agents becomes a challenge when one has a psychiatric condition being under psychotropic treatment, mostly due to metabolism site interactions regarding cytochrome P450 and pharmacological synergism of the common adverse effects [2].

Materials and Methods

We searched online studies published after 1 January 2020 in the PubMed database, using the following sentence: "psychiatric drug interaction COVID-19 medication", resulting in 31 studies. The exclusion criteria were set upon study information relevance. The standard PubMed Best Match sort is based on a weighted term frequency algorithm. This approach calculates the frequency with which terms appear in PubMed records. Those frequencies are then applied in a weighted manner to return a ranked list of PubMed citations that match your query terms. Therefore, after applying the exclusion criteria, 23 studies met the criteria following the searched sentence, of which one was a case-control study.

Results and Discussion

The literature highlights the high-frequency DDIs between antiviral agents and psychotropics, including antidepressants, antipsychotics, mood stabilizers and anxiolytics, ranging from interactions that are not clinically severe to those that produce life-threatening adverse drug reactions.

Antidepressants

Selective serotonin reuptake inhibitors

Fluoxetine, one of the most recommended SSRIs is metabolized by isoenzymes CYP2D6, CYP3A4, CYP2C9 and CYP2C19. A combination of ritonavir and fluoxetine or HCLQ and fluoxetine results in increased antidepressant serum concentration and is associated with potential ECG QTc prolongation. Fluoxetine has been reported to cause serotonin syndrome or serotonin toxicity and should be used with caution [3, 4, 8, 22]. However, some studies attribute fluoxetine a low/absent risk in co-administration with COVID-19 medication [5, 14].

Paroxetine, mainly metabolized by isoenzymes CYP2D6 and CYP3A4, with pharmacokinetic properties of protein binding up to 95%, make it susceptible to DDIs. An eloquent example is reported in a study where the co-administration of paroxetine and ritonavir/ fosamprenavir is associated with a low level of anti-depressant, an average of 55% due to protein displacement [3]. However, most studies highlight the important DDIs of paroxetine in co-administration with HCLQ or LPV/r, as in the plasmatic high concentration of antidepressant and potential ECG QTc prolongation [4, 5, 7, 16].

Escitalopram, although metabolized by the same iso-enzymes as previously described, reveals contradictory results. Three studies have found escitalopram with a low risk of DDIs in co-administration with antiviral drugs [5, 6, 8], while five studies have reported moderate to high risk in ECG QTc prolongation, especially when it is associated with HCLQ [3-5, 7, 11].

Sertraline undergoes CYP2D6 and CYP3A4 metabolism, in the process being also implied CYP2B6, CYP2C9 and CYPC19 isoforms. Probably because of this iso-enzyme heterogeneity the interaction with antiviral agents seems to be variable. Some studies have attributed the co-administration of sertraline and HCLQ an enhancing risk of hypoglycaemia [3] while others found either an overall low risk of DDIs with antiviral agents [5, 16], or a potential decrease of antidepressant serum concentration in association with ritonavir [4].

Fluvoxamine is a SSRI with moderate inhibitory properties over CYP3A4 isoenzymes [15]. Studies results have shown increased serum concentrations of antiviral agents such as HCLQ or ritonavir in the case of antidepressant associations [3, 8, 10, 11]. Although, there are a few studies that have found the co-administration of fluvoxamine and antiviral agents with a low risk of DDIs [5].

All study results have evidenced the low or absent DDIs of all SSRIs in co-administration with antiviral agents like favipiravir and remdesivir.

Serotonin-norepinephrine reuptake inhibitors

Often used as a second-line treatment especially for depressive disorders, anxiety disorders, but also for chronic pain syndromes, serotonin-norepinephrine reuptake inhibitors (SNRIs) represent a high potency pharmacological class being frequently prescribed in clinical practice. The main metabolism sites of the drugs are cytochrome P450 isoenzymes CYP2D6 and CYP 3A4, therefore, at least at a theoretical level DDIs are expected.

For venlafaxine, mainly metabolized by CYP2D6, CYP3A4 and CYP2C19 isoenzymes, the vast majority of studies draw the attention to be used with caution especially when it is co-administrated with HCLQ or LPV/r, due to the increased risk of QTc prolongation [3-5, 7, 11, 16].

Duloxetine, also metabolized by CYP2D6, but also by CYP1A2 seems to be safe for clinical use in co-administration with HCLQ or LPV/r. Most studies reported no major DDIs, but it is recommended to be monitored closely, due to antidepressant serum concentration variations [3-5, 8] also, in case of severe liver injuries due to an inflammatory state in COVID-19 infection, use of duloxetine must be avoided [9, 10].

Serotonin modulators

Trazodone, used for the treatment of major depressive disorder, anxiety disorder and obsessive-compulsive disorder, has a metabolism mediated through CYP3A4

and CYP2D6. The antidepressant's pharmacodynamics is characterized also by histamine H1 receptor and adrenergic alpha 1 receptor antagonism therefore, co-administration of trazodone and LPV/r is associated with antidepressant serum concentration elevation and serious potential life-threatening side effects such as marked sedation and hypotension, and syncope [3-5, 8, 11, 12, 16, 23].

Norepinephrine-serotonin modulators

Mirtazapine, metabolized by CYP1A2, CYP3A4 and CYP2D6, although it partially shares the same pharmacodynamic properties as the previous one, most studies haven't found major DDIs in co-administration with HCLQ or LPV/r [3, 8]. However, some studies have reported increased antidepressant serum concentration and potential QTc prolongation and increased sedation, therefore, if used, it is recommended to be monitored closely [4, 5, 11, 12].

Norepinephrine-dopamine reuptake inhibitors

Bupropion, a high potency antidepressant used to treat major depressive disorder and other mood disorders, is mainly metabolized by CYP2B6 isoenzyme. It seems that at this metabolism site, LPV/r has an increased induction effect, therefore, the co-administration of bupropion and LPV/r is associated with a decrease of antidepressant serum concentration as much as 50% [3-5, 8, 16, 17, 21].

Tricyclic antidepressants

First described in 1958 for the treatment of melancholic depression, the main metabolism site of these antidepressants are CYP2D6, CYP1A2, CYP3A4 and CYP1C19 isoenzymes. LPV/r's inhibitory CYP2D6 and CYP3A4 effects, make this co-administration problematic due to increased antidepressant serum concentrations and potential cardiac life-threatening side effects [4, 5, 7, 8, 11, 16].

No study reported DDIs when co-administering antidepressants and favipiravir or remdesivir.

There is some evidence regarding the safety of using antidepressants and the natural outcome of COVID-19 infection, overall, using antidepressants in patients with COVID-19 infection is associated with a slightly increased severe infection outcome [13].

Mood stabilizers

Lamotrigine

Most studies have concluded that dose adjustment is needed in the case of the co-administration of LPV/r, due to uridine diphosphate glucuronosyltransferase (UGT) enzyme induction, the mood stabilizers metabolism site. Some studies report serum concentrations decreasing up to 50% [3, 4, 8, 10, 11, 21]. No study reported DDIs at the co-administration of HCLQ.

Valproic acid

The metabolic pathway of this agent is heterogeneous because of its multiple enzyme sites of which: extensive UGT glucuronidation (UGT1A6, UGT1A9, UGT2B7), mitochondrial β-oxidation and minimal cytochrome P450 oxidation. Due to LPV/r induction properties on UGT, valproic acid serum concentrations decrease under concomitant use [3, 5, 11]. However, some studies recommend using with precaution valproic acid due to its possible problematic side effects such as bow marrow suppression, coagulation disorders, and liver toxicity [7, 9, 10]. One study reported LPV/r increased serum concentration in co-administration with valproic acid [4].

Carbamazepine

Frequently used in clinical practice, this agent is both a substrate and potent inducer of CYP3A4 isoenzymes. Therefore, antiviral agents such as HCLQ, LPV/r and RDV metabolized at this site present a lowering serum concentration in co-administration with carbamazepine [3, 4, 10]. Most studies recommend also precaution in the use of carbamazepine in infections management due to its liver toxicity side effects and potential bone marrow suppression, especially when co-administrated with a potent CYP3A4 inhibitor like LPV/r leading to elevated mood stabilizer serum concentrations [5, 7-9, 18, 20].

Lithium

Because of its pharmacokinetic properties, lithium remains un-metabolized and is excreted unchanged in the urine. However, because of its renal excretion necessity, most studies recommend precaution in its usage [7, 9, 20]. Some studies reported potential cardiac toxicity side effects in concomitant use of lithium and HCLQ or LPV/r [4, 5].

There is some evidence regarding the safety of using mood stabilizers/anticonvulsants and the natural outcome of COVID-19 infection, overall, using these drugs in patients with COVID-19 infection is associated with a slightly increased severe infection outcome, with higher rates for gabapentionoids [13].

Antipsychotics/Neuroleptics

First generation antipsychotics

Haloperidol. Being one of the most frequently used antipsychotic, study results show a high incidence of cardiac arrhythmias in co-administration of haloperidol with HCLQ, CLQ, or LPV/r and classifies the use of this antipsychotic at a moderate to high risk [3, 10, 12]. No interactions were found with favipiravir or remdesivir.

Chlorpromazine. First developed in 1951, chlorpromazine is one of the first antipsychotics discovered, being used with much less frequency than other first-generation antipsychotics. It is because of these considerations why few study results include chlorpromazine and antiviral SARS-CoV 2 agents in DDIs. Among these results, most studies report cardiac arrhythmias such as QTc prolongation [3, 11, 12].

Pimozide. Pimozide is a first-generation antipsychotic metabolized by CYP3A4 and CYP2D6 isoenzymes. All study results that include this antipsychotic conclude that the concomitant use with antiviral agents such

as HCLQ, CLQ, or LPV/r is associated with a high risk of elevated antipsychotic serum concentration and life-threatening cardiac arrhythmias [3-5, 10, 11].

Tiapride. Used in many European and Asian countries for alcohol withdrawal syndrome, study results show a moderate-high risk in association with HCLQ, CLQ, or LPV/r due to the potential life-threatening QTc prolongation [4, 5, 11, 12].

Second-generation antipsychotics

Olanzapine. Metabolized by both P450 cytochrome *via* CYP1A2 and glucuronosyltransferase, for olanzapine study results have evidenced the low risk of DDIs regarding life-threatening adverse effects. Because of its glucuronosyltransferase-mediated metabolism, the co-administration of olanzapine and LPV/r has been associated with lowering antipsychotic serum concentration up to 50%. No DDIs were reported for the association of HCLQ and olanzapine [4-6, 8, 10, 11, 16].

Quetiapine. Association of LPV/r results in high antipsychotic serum concentration because of the inhibitory properties of ritonavir over CYP3A4. The use of quetiapine in association with HCLQ or LPV/r is considered with high risk due to potential QTc prolongation [4, 5, 8, 11, 12, 16, 21].

Clozapine. One of the most effective antipsychotics used in the management of treatment-resistant schizophrenia, clozapine is associated with a moderate to high risk because of the multiple DDIs and overlapped metabolic toxicity. Clozapine is mainly metabolized by CYP1A2, CYP2D6, CYP3A4, but also suffers methylation and oxidation processes. Therefore, because of LPV/r inhibitory properties of the mentioned isoenzymes, the co-administration is associated with an increase in antipsychotic serum concentrations, QTc prolongation, increased metabolic side effects such as hyperglycaemia and hyperlipidaemia, high risk of neutropenia with a problematic clinical approach in the management of SARS-CoV-2 infected patients [3, 4, 7, 9-11].

Risperidone. Like the previous antipsychotics, risperidone has the same metabolism site and is associated with increased serum concentrations when co-administrated with LPV/r or HCLQ. Study results place the use of the antipsychotic at moderate risk, because of its potential QTc prolongation [3-5, 7, 22]. There was one study that reported cases of extrapyramidal symptoms and neuroleptic malignant syndrome when risperidone was associated with ritonavir [8].

Paliperidone. The major metabolite of risperidone is metabolized by the same isoenzymes: CYP2D6 and CYP3A4. Studies results have found a low to moderate risk of DDIs in the association of paliperidone and HCLQ or LPV/r, with potential ECG QTc prolongation and recommend precaution in usage especially in cases of SARS-CoV-2 infection associated with renal impairment [4, 5, 7, 9, 10, 12].

Aripiprazole. Appreciated for its dopamine D2 receptor modulator properties, aripiprazole metabolism is mediated by the same isoenzymes as the previous one. Study results are inconsistent, some results placing the antipsychotic at a low to moderate risk for the association with LPV/r of HCLQ because of the QTc prolongation [4-6], while other studies are placing aripiprazole as having the least potential of QTc prolongation in the co-administration with the same antivirals [10-12].

There is some evidence regarding safety using antipsychotics and the natural outcome of COVID-19 infection, overall, using antipsychotics such as aripiprazole, risperidone, olanzapine, or amisulpride in patients with COVID-19 infection is associated with an increased severe infection outcome [13].

Sedative/Anxiolytics/Hypnotics

Diazepam

Among the most commonly used benzodiazepines, diazepam is mostly metabolized by CYP3A4 and only a small ratio by CYP2C19. Co-administration of diazepam and LPV/r is associated with increased levels of benzodiazepine serum concentration, therefore most studies attribute the use of diazepam and LPV/r with moderate risk and recommend precaution and dose adjustment [3-5, 9, 19].

Alprazolam

Alprazolam shares with diazepam the same pharmacokinetic properties regarding its metabolism. Study results associate the use of alprazolam and LPV/r with moderate risks and like the previous observation regarding diazepam, if used, the recommendation stands for caution and dose adjustment [3-5, 8, 9, 19].

Lorazepam

A benzodiazepine different from the previous ones undergoes glucuronic acid conjugation in the metabolic processing, therefore almost all study results attribute a low risk of DDIs for the co-administration of lorazepam and LPV/r, HCLQ, FAVI, or RDV [4-7, 10, 12, 20].

Buspirone

A non-benzodiazepine anxiolytic with serotonin receptor modulating properties is mainly metabolized by CYP3A4 isoenzyme, therefore the co-administration of buspirone and LPV/r is associated with increased anxiolytic serum concentrations and overall moderate risks in clinical approaches [3-5, 8, 11, 19].

Zolpidem

This molecule is a non-benzodiazepine hypnotic mainly metabolized by CYP3A4, CYP1A2, CYP2D6, CYP2C9 and CYP2C19. The concomitant use of zolpidem and an inhibitor of CYP3A4 such as LPV/r is associated with increased hypnotic serum concentrations. Therefore, because of the increased risk of sedation, studies results place zolpidem at moderate risk of DDIs [3-5, 7, 9].

No study results reported DDIs between any psychotropic mentioned in this section and HCLQ, FAVI and RDV.

There is some evidence regarding the safety of using sedative/anxiolytics and the natural outcome of COVID-19 infection, overall, using sedative/anxiolytics in patients with COVID-19 infection is associated with a slightly increased severe infection outcome [13].

Conclusions

The clinical approach for psychiatric patients infected with COVID-19 undergoing antiviral treatment is a challenge at least due to the numerous interactions between psychotropic and antiviral medication, in terms of common metabolism pathway, but also synergistic side effects.

Conflict of interest

The authors declare no conflict of interest.

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