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Consultation psychiatry in COVID-19 patients: Lopinavir/ritonavir interactions with main psychiatric drugs

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Within only about 7 months from its appearance, COVID-19 has rapidly spread across the globe, infecting (at the time of writing) more than 62 million worldwide and causing the death of more than 1 455 030 persons.[1] Several extant antivirals have been investigated as potential treatment options for COVID-19, including a combination of protease inhibitors lopinavir/ritonavir.[2] Front-line COVID-19 physicians should be well aware that the use of these drugs requires particular attention due to their possible adverse effects on the central nervous system, especially in the treatment of psychiatric patients and the vulnerable elderly population, characterized by many comorbidities and co-treatments.

In light of the above, the aim of this Letter is to briefly describe the possible interactions between lopinavir/ritonavir and psychotropic drugs.

Protease inhibitors are all metabolized in the liver by the cytochrome P450 (CYP) enzyme system, especially the CYP3A4 isoenzyme.[3] The CYP system is also the major hepatic enzyme complex involved in the metabolism of many other drugs, including most of the psychotropic drugs used in clinical practice. Its various isoenzymes can be either induced or inhibited by a number of agents and the protease inhibitors, particularly ritonavir, are among the most potent inhibitors of CYP3A4.[4] Ritonavir also has high inhibition potency against CYP-2C9, -2C19, and -2D6.[5] Moreover, it is also an inducer and inhibitor of p-glycoprotein.[6] This could lead to clinically relevant pharmacological interactions that physicians, when called on to deal with COVID-19 patients, must consider. Much of the data on drug interactions with protease inhibitors appear in product labeling information and in a few case-report studies, but many more pharmacological interactions and resulting clinical indications can be inferred from the pharmacokinetics and pharmacodynamics of psychiatric medications (see Table S1 and the references). There are different mechanisms by which lopinavir/ritonavir interact with psychiatric treatments (antidepressants, antipsychotics, and mood stabilizers):

1 *Inhibition of the cytochrome P450 isoforms implicated in the metabolism of psychoactive drugs*. This inhibition can reduce the clearance of many antidepressants, antipsychotics, and anxiolytics, increasing plasma concentrations of the main molecules and related major active metabolites that, in turn, will be able to exert therapeutic or collateral effects depending on the level and type of inhibition.In this mechanism, all protease inhibitors are involved but, for the reasons mentioned above, ritonavir is obviously the main actor. It is responsible for the main psychiatric contraindications indicated in the product labeling information (i.e., lurasidone, pimozide, quetiapine, midazolam, and triazolam) through its strong inhibition of CYP-3A4 but many other clinically relevant interactions with antidepressants and antipsychotics have been described in the literature[7] and many others can be deduced.Almost all monoaminergic modulators, such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants, can be affected by these interactions (see Table S1).
2 *Induction of the cytochrome P450 isoforms implicated in the metabolism of psychoactive drugs*. This induction can increase the clearance of different drugs, decreasing their plasma concentrations and, probably, the resulting clinical efficacy. Ritonavir has been shown to induce CYP-2B6 (e.g., bupropion), CYP-1A2 (e.g., olanzapine), and UDP-glucuronyltransferases (e.g., lamotrigine and valproate; see Table S1).
3 *Induction of the cytochrome P450 isoforms implicated in the metabolism of antivirals and reciprocal effects*. Protease inhibitors are also substrates of cytochrome activities and their levels can be modulated by inhibitors or inductors. Lopinavir levels and other antivirals can be decreased by different inducers.In the psychiatric context, the principal agent is *Hypericum perforatum* (St. John's wort), a herbal medicine used for its possible antidepressant activity and a potent inducer of CYP-3A4. Coadministration with St. John's wort may significantly reduce the plasma concentrations of HIV protease inhibitors and result in a potential loss of virologic response.[8] Coadministration with carbamazepine was reported to be particularly complex and unpredictable, as its induction on CYP-3A4 is potentially able to decrease protease inhibitor concentrations with the resulting potential antiretroviral resistance and treatment failure, and its levels may, at the same time, be boosted by ritonavir leading to carbamazepine-related toxicity[9] (see Table S1).
4 *Greater risk of QT prolongation*. Protease inhibitors could predispose individuals to QT prolongation and torsade de pointes[10] by dose-dependent block of human ether-a-go-go-related gene (*HERG*) potassium channels. Theoretically, coadministration with other agents that can prolong the QT interval – and the psychiatric pharmacopeia is full of QT prolongers – may result in additive effects and increased risk of ventricular arrhythmias, including torsade de pointes and sudden death.

Disclosure statement

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Supporting Information.

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Obsessive–compulsive disorder and related symptoms amidst the COVID-19 outbreak: Results from the COLLATE project

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Studying obsessive–compulsive disorder (OCD) symptoms amidst the COVID-19 pandemic is important for three major reasons. First, health anxiety can be prevalent in OCD, and exacerbated in the prevailing climate.[1] Second, OCD can develop in response to traumatic events.[2] Third, revised health guidelines have likely normalized certain compulsions (e.g., repeated handwashing). These behaviors may extend to the general population, including fears about becoming ill or infecting others with COVID-19. Few studies have explored OCD amidst previous outbreaks of pandemics. Retrospective analysis of an electronic mental health database concluded that patients with OCD were overrepresented in those expressing moderate to severe swine flu concerns.[3] Another study demonstrated that OCD symptoms significantly predicted swine flu fears in a student cohort.[4] Pertaining to COVID-19, an online survey found higher endorsement of OCD symptoms in medical, relative to non-medical, workers.[5] Having an organic disease was an overall risk factor for OCD symptoms, with being female, rural living, and potential COVID-19 exposure as added risk factors for medical workers.

Our current study aimed to: (i) document COVID-19 concerns in an OCD group relative to a matched general population (GNP) group; (ii) compare group members' mental health status, including negative emotions; and (iii) explore endorsement of OCD-related behaviors and associated predictors. We hypothesized that the OCD group would assign higher rankings for concerns related to becoming ill with COVID-19, and be significantly more depressed, anxious, and stressed relative to the GNP group. These analyses utilized cross-sectional data from Waves 1 (April) and 2 (May) of our COVID-19 and You: Mental Health in Australia Now Survey (COLLATE). The project design has been published elsewhere.[6] A description of methodology and data analyses, including participant matching (and psychiatric comorbidity in the OCD group in Table A), is summarized in Appendix A.

Table 1 shows the top 10 COVID-19 concerns by group in Wave 1. The top two concerns were identical across groups and related to 'a loved one dying or being infected with COVID-19.' Notably, 'oneself dying or being infected with COVID-19' was ranked lower in the OCD group relative to the matched GNP sample. The OCD group did, however, place 'implications for health and well-being of self' above that of their 'family and loved ones,' with the opposite pattern found for the GNP group. Group-wise comparisons of mental health in Wave 1 revealed that the OCD group reported significantly increased depression, anxiety, and stress as well as poorer quality of life relative to the GNP group, with large effect sizes. *Severe* depression and anxiety, and *moderate* stress were more likely in the OCD group, with *mild* depression more likely in the GNP group (see Appendix B and Table B, which also characterizes groups by sociodemographic information and COVID-19-related lifestyle changes).

When these analyses were rerun for Wave 2, the top 10 themes remained largely similar, with a few exceptions (Appendix C and Table C). However, a trend towards poorer mental health was observed: *extremely severe* depression, anxiety, and stress were more likely in the OCD group, whereas *moderate* depression, *mild* anxiety, and *moderate* stress were more likely in the GNP group (Appendix D and Table D1). Notably, washing, checking, and obsession scores did not appear significantly elevated (relative to the original validation study[7]; Table D2). Regression analysis revealed that distal, $F(5, 612) = 10.3$, $P < 0.001$, $r^2 = 0.078$, and proximal, $F(14, 612) = 35.9$, $P < 0.001$, $r^2 = 0.379$, factors significantly predicted OCD symptoms across the entire Wave 2 cohort (Appendix E and Table E). Only age, education, and having an existing medical condition were significant predictors in Block 1 (distal), but were no longer significant in Block 2 (proximal); these were mediated by depression, anxiety, and stress, which served as unique predictors for OCD symptoms.

Our hypothesis was partly supported in that though the OCD group did not assign higher rankings for concerns related to becoming ill from COVID-19, significantly increased negative emotions were reported relative to the GNP group. When coupled with the finding that negative emotions were significantly associated with OCD symptoms, this suggests that the mental health of persons with OCD may be more adversely affected in the longer run. Study limitations included relying on self-reported OCD, and the inability to perform statistical comparisons between our two data waves (owing to unequal group sizes and few repeat respondents). Previous pandemic research has suggested delayed and prolonged mental health impacts, with time lags from pandemic onset to manifestation of psychopathology.[8] Applying this reasoning, we infer that if effective interventions to address elevated negative emotions are not enacted in a timely manner, OCD symptoms may significantly worsen as the outbreak continues to unfold. This is the challenge that existing mental health-care systems need to address.

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