Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Interactions of recommended COVID-19 drugs with commonly used psychotropics

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Sir,

As COVID-19 pandemic has spread all over the world and patients' number is escalating (Tandon, 2020), different statutory bodies like Centers for Disease Control (CDC), Govt. of India and other apex institutes have come out with different guidelines for managment of COVID-19 (Govt of India, 2020; Sanders et al., 2020). Ritonavir/Lopinavir, Hydroxychloroquine (HCQ) and Azithromycin are recommended either as a single agent or in combination for duration of 5–10 days for treatment of COVID-19. In view of above and the magnitude of COVID-19 morbidity, it is pertinent to discuss the interaction of these drugs with commonly used psychotropic medicines (Chatterjee et al., 2020).

The most significant side effect which is common for all the COVID-19 recommended drugs (highest risk with HCQ) is QTc prolongation, which many psychotropics are also notorious for (Table 1) (Beach et al., 2018). Therefore, combination of these drugs can prove lethal if adequate precautions are not excised. Baseline ECG to check for QTc is a must in these situations. If QTc is more than 440mSec in males or 470 mSec in females then there is risk of developing cardiac arrythmia. Olanzapine and aripiprazole are considered to have least QTc prolongation, so these two at lowest possible dose may be considered if need arises, and injectable forms of any antipsychotic should be avoided.

There are few other specific points which are discussed below.

Hydroxychloroquine is known to cause seizure, neutropenia, and myocardial toxicity. Clozapine also has similar side effect profile (Haas et al., 2007). So, concomitant use of the two can be fatal and best avoided.

Ritonavir/Lopinavir are contraindicated if patient is on Lurasidone or Pimozide, according to FDA, as it may cause life threatening cardiac arrhythmias. These protease inhibitors (PI) are potent CYP3A4 inhibitors, so any psychotropic which is metabolized mainly through CYP3A4 (Buspirone, Clonazepam, Carbamazepine, Lurasidone, Quetiapine, Mirtazapine, Trazodone) should be dose adjusted or stopped. Due to above reason, when administered with midazolam, it can cause prolonged respiratory depression and with sildenafil it can cause persistent erection. Moreover, PIs are themselves substrates of CYP3A, so any psychotropic that inhibits (Fluvoxamine) or induces (Carbamazepine, Topiramate) CYP3A are better replaced with alternative drugs (English et al., 2012). Ritonavir/Lopinavir, by inducing glucuronidation in liver reduces serum levels of Valproate and Lamotrigine; so appropriate dose adjustments of these anticonvulsants are required, preferably with serum level monitoring (Sheehan et al., 2006). FDA recommends reducing the dosage of Quetiapine to 1/6th and to monitor for Quetiapine related adverse effects. If the patient is on disulfiram, it can cause disulfiram reaction as the combination oral solution (not capsule) of Ritonavir/Lopinavir contains 42.4 % ethanol (v/v) alcohol (Cvetkovic and Goa, 2003). Ritonavir/Lopinavir can cause metabolic side effects, which is caused by second generation antipsychotics too. But this is not of great significance as COVID-19 approved drugs are given only for short term.

Azithromycin, besides its QTc prolonging property, can also cause acute and transient increases in liver aminotransferase in 1–2 % of cases and there are anecdotal reports of liver injury, so should be used cautiously in patient on valproate with regular monitoring of liver function tests.

Remdesivir, an investigational RNA polymerase inhibitor, is recently authorized for emergency use in severe cases of COVID-19. So, there is no data regarding its interaction with psychotropics. However, it can cause elevated liver enzymes (FDA, 2020) which means drugs like valproate and benzodiazepines should be used with caution.

To summaries, the area of drug-drug interactions of COVID-19 recommended drugs and psychotropics is very relevant in current scenario. Most important and significant interaction is with respect to QTc prolongation followed by CYP3A inhibition. Clinicians need to have in-depth understanding of these interactions when treating a COVID-19 positive patient who is also on psychotropic medications.

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Table 1
Psychiatric drugs with high risk of QTc prolongation.

First generation antipsychotics:	Thioridazine, Haloperidol, Pimozide, Chlorpromazine.
Second generation antipsychotics:	Quetiapine, Iloperidone, Ziprasidone, Clozapine.
Selective Serotonin Reuptake Inhibitors:	Escitalopram
Tricyclic Antidepressants:	Amitritilline, Nortryptilline, Imipramine, Clomipramine, Imipramine
Serotonin Norepinephrine Reuptake Inhibitor:	Venlafaxine
Other antidepressant:	Mirtazapine

Declaration of competing interest

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