Psychiatric implications of the use of hydroxychloroquine in COVID-19 patients

Sir,

Chloroquine and hydroxychloroquine (HCQ) have emerged as a treatment option for the coronavirus disease 2019 (COVID-19) infection. The intake of these drugs becomes more important for patients with mental disorders, who may already be on psychotropic medications. Accordingly, mental health professionals need to understand the psychiatric and cardiac side effects of chloroquine and HCQ. In terms of cardiac side effects, prolongation of the QTc interval is one of the most talked-about and fatal side effects, which can lead to sudden cardiac death. This side effect is essential from the perspective of mental disorders because antipsychotics are well known to cause QTc prolongation. The risk factors for QTc prolongation include hypokalemia, hypocalcemia, loop diuretics, antiarrhythmic drugs, and the use of QTc-prolonging drugs of list 1 of CredibleMeds.[1] Accordingly, mental health professionals while using various psychotropic medications should always inquire about the use of HCQ and chloroquine.

In addition, the mental health professional should also inform their patients who are already on psychotropics about the increased risk of QTc prolongation, especially when HCQ/chloroquine is added to the ongoing psychotropic medications. A combination of psychotropics with HCQ can be lethal and should be prescribed with caution. To prevent a fatal outcome, baseline electrocardiogram (ECG) should be done in all such cases and regular ECG monitoring should be done for patients who are on HCQ and antipsychotics.[2]

Another issue that mental health professionals must be aware of is the neuropsychiatric effects of chloroquine/HCQ. There is limited literature in the form of case reports, with regard to the neuropsychiatric side effects of chloroquine/HCQ. The neuropsychiatric effects of these drugs are rare, with the estimated risk ratio of 1:13,600.[3]

In terms of neuropsychiatric side effects, the first case of chloroquine-induced psychosis was reported in 1958.[4] Available literature also suggests the use of chloroquine to be associated with the development of psychosis, personality change, depression, suicidal ideations/suicidal behavior, anxiety disorders, and delirium.[5,6] The disorders of thought, memory, attention, and behavior have also been reported with the use of 4-aminoquinolines (chloroquine and HCQ).[6-9] Some of these side effects, such as delirium, are related to toxicity.[10] However, most of these data are related to chloroquine, and little information is available for neuropsychiatric side effects of HCQ. The adverse effects of HCQ usually appear with high doses (6 mg/bodyweight/day) or in the presence of other flavoring elements (pharmacokinetic interactions, personal and family psychiatric history, and the disease for which HCQ is used). HCQ is more polar and less lipophilic than chloroquine. The diffusion of HCQ across the cell membranes is difficult as compared with chloroquine.[11] However, despite this, the neuropsychiatric side effects of HCQ cannot be completely ruled out. The possible HCQ-induced neuropsychiatric side effects depend on its ability to cross the blood–brain barrier. In the brain, HCQ can have a tissue concentration 10–20 times higher than a plasma concentration.[11]

The neuropsychiatric side effects are considered to occur at all ages, during acute or chronic use, with and without a history of mental illness.[11-14] It has been seen that symptoms resolve after stopping the drug but would not resolve quickly and would take weeks or months.[15]

Another issue is the drug interactions between chloroquine/HCQ and psychotropics at the pharmacokinetic level. The major metabolic enzymes of chloroquine include cytochrome P450 and isoenzymes (CYP) CYP2C8 and CYP3A4/5.[16] HCQ is a substrate of CYP2C8, CYP3A4/5, and CYP2D6, as well as an inhibitor of CYP2D6. The main CYP isoform involved in the metabolism of HCQ is CYP3A4. Thus, HCQ may be a substrate of kinetic interactions with inducers and inhibitors of CYP3A4. Several psychotropic medications are potent inhibitors of CYP2D6 (e.g., fluoxetine and paroxetine) and can increase the levels of HCQ. HCQ appears to inhibit CYP2D6 and can affect the levels of psychotropic medications dependent on CYP2D6 for their metabolism.[17] These include aripiprazole, atomoxetine, paroxetine, risperidone, several tricyclic antidepressants, venlafaxine, and vortioxetine.
Another side effect of HCQ, which may be important to remember while using psychotropics, includes a reduction in seizure threshold, as many psychotropics are also associated with a decrease in the seizure threshold,[18] with the most notable being clozapine and chlorpromazine.

Accordingly, in the era of COVID-19, when a patient presents with new-onset psychiatric manifestations, psychiatrists should always inquire about the ongoing medications, especially chloroquine/HCQ. If such a history is present until otherwise proven, the psychiatric manifestations should be evaluated as drug-induced disorders. Hence, the detailed history of temporal correlation of the onset of symptoms and the use of these medications needs to be evaluated. If such an account is clearly available or doubtful, before instituting psychotropic medications, it would be advisable to stop the implicated medications and closely monitor the psychiatric manifestations. If the symptoms are severe enough to require the use of psychotropics, usually use psychotropics, on as and when required basis should be considered, rather than regular use of psychotropics, with proper counseling of the patient and the family members about the risk of QTc prolongation. Before starting psychotropics, baseline ECG should be done and the QTc interval should be monitored from time to time.

Further, it can be said that it is always advisable to assess the mental state of the patients, before starting HCQ/chloroquine in patients with COVID-19. In fact, it should be advised that in all the trials of HCQ in COVID-19 patients, psychiatrists should be included as experts to assess the mental state at the baseline, throughout the therapy, and possibly after the completion of HCQ therapy. For any new-onset psychiatric syndrome, the history of use of HCQ should be reviewed and while prescribing psychotropics, the risk of prolongation of QTc with the combination should be kept in mind.

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Conflicts of interest
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