Hydroxychloroquine and chloroquine for COVID-19: psychiatric aspects of patient safety considerations

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Although a few months have passed since the onset of the novel coronavirus 2019 disease (COVID-19), there is still no definite preventive and therapeutic approach for this illness. Numerous antiviral agents, immunotherapies, and vaccines are being investigated in a compassionate-use cohort.[1] Searching for effective and safe therapies for COVID-19 infection is a complex challenge for scientists. Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalarial agents with anti-inflammatory and immunomodulatory activities. These drugs have gained significant interest for the management of COVID-19. Several authors[2,3] have demonstrated potent *in vitro* activity of CQ against SARS-CoV-2, ARS-CoV-1, and MERS-CoV. HCQ, which differs from CQ by the presence of a hydroxyl group in place of one of two terminal methyl groups in the side chain, has long been used in rheumatological disorders owing to its better tolerability than CQ. The initial few uncontrolled, open-label studies of HCQ have reported control of pneumonia, improvement in lung imaging, reduction of viral load, and shortening of the disease course.[4,5] There are so far few randomized controlled trials available to assess the efficacy of HCQ or CQ, with inconsistent results.[6] Moreover, in other viral infections, CQ has demonstrated an apparent discordance between its *in vitro* efficacy and its lack of observed *in vivo* or clinical effectiveness,[7] which may be true for HCQ also.

HCQ and CQ have long been known to potentially cause neuropsychiatric adverse effects including psychosis, also known in the literature as psychosis following chloroquine (PFC).[8] Usual side effects of CQ or HCQ are gastrointestinal upset, headache, blurring of vision, pruritus, urticaria, and photosensitive skin lesions.[8] Although psychiatric symptoms from CQ or HCQ often resemble a brief psychotic or delusional disorder, on careful evaluation they are more likely to feature visual hallucinations, derealization, restlessness, agitation, and anxiety.[8] Quinoline drugs such as CQ or HCQ may induce such psychiatric effects with use irrespective of their indication (e.g. arthritis, amoebic abscess, systematic lupus erythematosus, and malaria).[9] It is likely that with use of HCQ or CQ in COVID-19, at least in some patients, similar episodes of psychosis and other psychiatric effects will be observed. Unfortunately, the assessment of such psychiatric adverse reactions has not been adequately addressed in studies performed to date for use of HCQ or CQ against COVID-19.[6] Complicating matters further, there are reports of COVID-19 independently causing neuropsychiatric symptoms possibly as a result of an infectious encephalopathy or from cerebrovascular complications or hypoxemia, with some patients presenting seizures and impaired consciousness.[10] In addition, although HCQ/CQ may induce psychosis and other neuropsychiatric effects more commonly at higher dose, the range of dosing used empirically against COVID-19 has been associated with the onset of such symptoms, including doses of CQ as low as 300 mg.[8]

This side effect of CQ/HCQ is proposed to be due to disturbed lysosomal function in immature neurons and cell death due to disruption of mitochondrial membrane potential.[11] Moreover, the COVID-19 pandemic is a major threat nowadays to health, social welfare, and the global economy. A traditional stress–vulnerability model for the development of CQ- or HCQ-induced psychosis in the face of such a huge stress may be applicable as is suggested in the case of amphetamine and psychosis (Figure 1). Some users of HCQ will not develop psychosis even using a high dose, while others will develop psychosis with a single dose. Vulnerability includes past and strong family history of psychosis,[8] but not race, nutritional status, or organ failure (moderate).[12] In fact PFC is

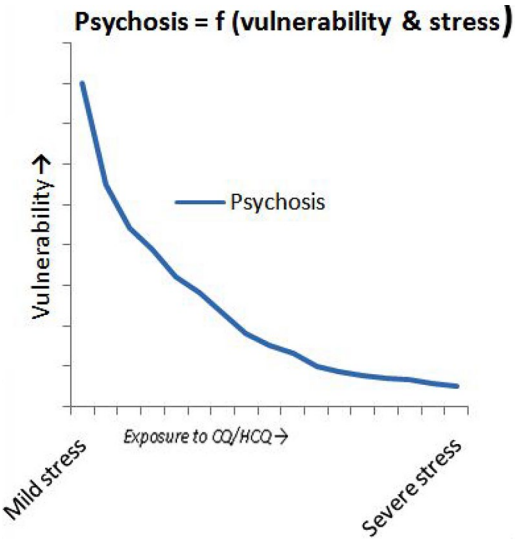

Figure 1. The traditional stress–vulnerability paradigm.
CQ, chloroquine; f, function of; HCQ, hydroxychloroquine.

reported less frequently from developed countries, because HCQ or CQ have rarely been used there before the COVID pandemic.

The efficacy studies of HCQ in patients with COVID-19 have rarely included severely ill patients in the ICU who receive several other medications and have organ failure.[6] In addition, when HCQ is combined with azithromycin, the chances of cardiac complications (e.g. QTc prolongation and arrhythmias) are increased.[13,14] Although both cardiac and neuropsychiatric adverse effects are rare (incidence is 1 in 1181 patients and 0.09%, respectively),[15] in other indications, its incidence can be high when these drugs are used rampantly in patients with COVID 19.

Given the unproven benefit of use of HCQ and CQ, and the potential for misattribution of symptoms, it may be appropriate to restrict use of the drugs against COVID-19 patients who are already suffering from psychiatric illness or who have a history of such illness, or cardiac conduction problems (e.g. sick sinus syndrome etc), or who are already taking psychotropic medication, which is known to prolong QTc. Some authors caution against solely relying on these efficacy data to support indication and dosing regimens for patients with COVOD 19. Magnetic resonance imaging (MRI) brain scan, electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis should be the routine screening tools in such patients. In cases where HCQ or CQ are used against COVID-19, the physician or psychiatrist should closely monitor for psychiatric symptoms, and maintain a high level of suspicion that any such effects, including symptoms of psychosis, may represent an adverse reaction to the drugs.

Author contributions

Both authors contributed equally to this work.

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