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

Safety considerations for chloroquine and hydroxychloroquine in the treatment of COVID-19

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To the Editor

Based on a demonstrated *in vitro* effect on SARS-CoV-2 and its known safety profile, both chloroquine and hydroxychloroquine (CQ/HCQ) are currently being used off label to treat COVID-19 [1]. However, although the safety of CQ/HCQ is well established in malaria or autoimmune disease, COVID-19 patients could be more vulnerable to side effects because of their advanced age, comorbidities (such as diabetes, obesity and cardiovascular disease), and subsequent co-medication [2]. Both agents are metabolized via the liver and the kidney. Critically ill patients may have an altered metabolism due to changes in hepatic and renal function, which could increase the risk of adverse reactions. Additionally, there may be interactions with co-medication normally not taken together with CQ/HCQ. Both drugs have long half-lives (approximately 1–2 months) and distribute poorly in fat tissue [3]. Therefore, long-term monitoring for adverse reactions is recommended. Importantly, CQ/HCQ have narrow therapeutic ranges, and toxic effects are closely related to the ingested dose. A one-time dose of 20 mg/kg CQ has been described to be toxic, and doses of 30 mg/kg CQ have resulted in case fatalities [4]. Apart from the general safety profile of CQ/HCQ, there are adverse reactions that may interfere with the clinical picture of COVID-19 due to their similarity to the symptoms of the illness. In particular, this holds for cardiovascular, neuropsychiatric and gastrointestinal adverse drug reactions. Table 1 illustrates the five most commonly reported suspected adverse drug reactions in these organ classes, as reported to the global pharmacovigilance database of the WHO (VigiAccessTM) [5]. This global database provides insight into spontaneous post-marketing case safety reports on suspected adverse reactions. The data should be interpreted with caution as the number of reports may be influenced by many different factors, including patients' baseline characteristics, extent of exposure, and nature of adverse reactions. Reported cardiac side effects of CQ/HCQ include conduction disturbances (bundle-branch block, incomplete or complete atrioventricular block, QT prolongation and subsequent torsade de pointes) and cardiomyopathy (hypertrophy and congestive heart failure). Due to their systemic infection and comorbidities, COVID-19 patients appear to have a higher risk of cardiac arrhythmia, QT prolongation and myocardial damage *a priori* [6]. This could result in the cardiotoxicity of CQ/HCQ being of particular importance, especially when given in combination with other QT-prolonging agents like azithromycin [7]. Neurological and psychiatric side effects have also been reported following CQ/HCQ treatment. Neurological side effects include muscular weakness, diplopia, dyskinesia, seizures, myasthenic syndrome, and (with long-term use) neuromyopathy. Psychiatric side effects include sleeplessness, agitation, psychosis, depression, anxiety, aggressiveness and confusion; psychiatric side effects start within a few days after the beginning of treatment and improve after cessation of treatment. COVID-19 patients suffer from dyspnoea, which may in turn lead to anxiety and sleeplessness, symptoms that may be aggravated by potential psychiatric side effects of CQ/HCQ. Finally, gastrointestinal symptoms (nausea and diarrhoea) have been reported and are the presenting complaint in some cases. In 393 patients admitted to two hospitals in New York, diarrhoea and nausea or vomiting were reported in 23.7% and 19.1% of patients, respectively. To these patients, treatment with drugs having potential gastrointestinal side effects could be problematic [2].

In conclusion, it is likely that some of the commonly reported adverse effects of CQ/HCQ will hamper successful treatment of patients suffering from COVID-19. Thus, until adequately powered randomized controlled trials (RCTs) provide more information on

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Table 1
Relative frequencies (%)[a] of the most commonly reported suspected adverse drug reactions as registered in the WHO pharmacovigilance database (www.vigiaccess.org) for system organ classes considered relevant to patients with COVID-19 (access date April 9, 2020)

	Chloroquine	Hydroxychloroquine
Cardiac disorders	Tachycardia (1.6%), cardiomyopathy (0.7%), palpitations (0.6%), cardiac arrest 0.6%), atrioventricular block complete (0.5%)	Cardiomyopathy (0.7%), palpitations (0.6%), cardiac failure (0.4%), tachycardia (0.3%), cardiac failure congestive (0.3%)
Gastrointestinal disorders	Vomiting (10.5%), nausea (8.4%), diarrhoea (4.5%), abdominal pain (3.5%), abdominal pain upper (2.5%)	Nausea (5.3%), diarrhoea (3.6%), abdominal discomfort (2.4%), vomiting (2.3%), abdominal pain (1.3%)
Psychiatric disorders	Anxiety (2.1%), depression (2.0%), psychotic disorder (1.5%), hallucination (1.1%), insomnia (1.1%)	Insomnia (0.7%), depression (0.6%), anxiety (0.4%), completed suicide (0.3%), sleep disorder (0.3%)
Nervous system disorders	Headache (7.8%), dizziness (5.2%), seizure (2.8%), balance disorder (1.6%), neuropathy peripheral (1.2%)	Headache (2.8%), dizziness (2.1%), visual field defect (0.6%), paraesthesia (0.6%), hypaesthesia (0.6%)

[a] Relative frequencies (%) were calculated by dividing the absolute number of adverse reaction reports by the total number of adverse reaction reports for each drug. For chloroquine and hydroxychoroquine VigiAccessTM contains a total of 5797 and 22138 records, respectively.

the efficacy and safety of CQ/HCQ use in the treatment of patients with COVID-19, it is very important that the potential benefits of these agents are weighed against the potential risks. Furthermore, clinical trials should also evaluate the long-term (e.g. 3–6 months post-therapy) (side) effects of the use of CQ/HCQ in COVID-19, such as cardiomyopathy, muscle weakness, anxiety, sleeplessness and gastrointestinal disorders. Preferably, until data from RCTs become available, the off-label use of CQ/HCQ should be reserved only for COVID-19 patients treated in context of clinical trials in order to improve our knowledge on safety and efficacy.

Author contributions

The text was written by SG, EW and CN. MK collected and added the pharmacovigilance data. All authors reviewed and revised the manuscript.

Transparency declaration

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