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Letter to the Editor

Psychiatric adverse events with hydroxychloroquine during COVID-19 pandemic

The directives and evidence concerning drugs for the treatment and prophylaxis of Covid-19 are rapidly evolving. COVID-19 is now pandemic and recent publications in the Asian Journal of Psychiatry have fruitfully synthesized the impact of the pandemic on mental health (Mukhtar, 2020; Rajkumar, 2020; Tandon, 2020; Zhao and Huang, 2020). In such a context and given the worldwide experience, it is notable that the mental health of frontline health care providers is affected (Mohindra et al., 2020).

With this pandemic, some people receive hydroxychloroquine (HCQ) either as a treatment or as a prophylaxis (Abena et al., 2020; Colson et al., 2020; Cortegiani et al., 2020, ICMR 2020, Liu et al., 2020; Rathi et al., 2020). Precautions have to be taken because of the psychiatric vulnerability in some individual and the side effects of this drug (Juurlink, 2020; Stip, 2020; Touret and de Lamballerie, 2020). For instance, the FDA has authorized clinicians to prescribe chloroquine and hydroxychloroquine for patients admitted to hospital with covid-19, and in parallel there were warnings from scientific advisors that no randomized controlled trial has been completed to date to support the drugs’ safety and efficacy in this COVID-19 population (Lenzer, 2020, Owens 2020). The latest directives from both the US FDA and now Health Canada indicate that there is no evidence that HCQ is effective against Covid-19. Moreover the drug is contraindicated by these agencies for use against Covid-19 due to risk of heart arrhythmias. The guidelines from India are in contra-indication to Canadian and US guidelines. In vivo evidence for efficacy of HCQ for treatment of COVID-19, and prophylactic efficacy is inferred from therapeutic efficacy. We illustrate this situation with this case.

A 25-year-old Canadian nurse patient comes to consult because she is anxious. She tested positive for COVID-19 and she finished quarantine. She had only a simple sore throat and a feverless headache. She recovered very well. She no longer works in the emergency of her hospital but plans to make herself useful by joining a health NGO in Haiti being a malaria endemic area. The patient had never received anti-malaria treatment, had no history of malaria, no toxic habits, and no allergies. She had started on chloroquine antimalarial chemoprophylaxis - 400 mg once a week thereafter) for asymptomatic health-care workers treating patients with suspected or confirmed COVID-19 (ICMR 2020, Rathi et al., 2020). In her antecedents she reported a psychotic episode 2 years ago after having stayed in Haiti for 3 weeks. She had started on chloroquine antimarial chemophrophylaxis - Haiti being a malaria endemic area. The patient had never received anti-malaria treatment, had no history of malaria, no toxic habits, and no allergies. She had started treatment a week before departure by taking a 300 mg tablet on Monday and Thursday. The chemoprophylaxis was supposed to be 4 weeks after her return. No incidents were reported in Haiti 48 h after her returned, the patient presented behavioural problems with agitation. The patient was admitted and mental exam revealed a conscious patient without neurological deficit but with temporal disorientation. She was fever-free, normal blood pressure. No discussion was possible with the patient who presented tachypnoea, incoherent speech with delusional syndrome, logorrhea with echolalia, insomnia and psychomotor agitation. The blood count, electrolytes, kidney, hepatic function, glycemia were normal, the thick smear microscopy was negative, no biological inflammatory syndrome, urine drug screen negative, as well as the CT scan, EEG and ECG. The chloroquine level was 0.5 mg / L. Chloroquine was stopped. Evolution was good after an 8-day stay in the psychiatric ward. She received olanzapine 7.5 mg 5 days and the episode was attributed to a psychiatric adverse event (PAE). Before going to India, the patient wants to be reassured and get evidence-based information.

Chloroquine is used to prevent and treat malaria. The addition of a hydroxide derivative to chloroquine made it possible to have less AE often with HCQ (Liu et al., 2020). For many years, both drugs have been used for treatment and prophylaxis of malaria and treatment of, such as systemic lupus erythematosus, rheumatoid arthritis and sarcoidose. HCQ and chloroquine have similar pharmacokinetic properties, with high oral bioavailability and tissue penetrance, partial hepatic metabolism, and high volumes of distribution as they diffuse into adipose tissue. Hydroxychloroquine has also attracted attention as a possible treatment or prophylaxis for the COVID-19 (Mitja and Clotet, 2020). In recent years, biological and clinical work has shown that beyond its anti-inflammatory and immunomodulatory action, hydroxychloroquine can improve the risk vascular by acting directly on the lipid profile and has antithrombotic property (Frimpong et al., 2018). It shows also an in vitro antiviral activity against a range of RNA viruses. Its mechanism of action is likely acting via the golgi vesicle, lysosome pH increase. Psychiatric side effects could be related to the cholinergic imbalance and to the down regulation of P-glycoprotein.

To answer the patient, a literature review was performed using PubMed and Scopus to identify relevant all-language articles published through April 2020. Search terms included various psychiatric symptoms or side effects (depression, anxiety, psychosis) and hydroxychloroquine. Search terms for relevant publication types (case reports, case series, RCTs, systematic reviews and meta-analysis) were also included (See Table 1). We found 113 relevant case reports, 12 systematic reviews/meta-analysis and 18 RCTs. Additional relevant articles were identified from the army registry from different countries (France, Korea, Uganda, Italy, UK USA) (Migliani et al., 2014; Kotwa et al., 2005; Duparc et al., 2020, Touze2001; Touze et al., 2007; Yeom et al., 2005). Active clinical trials were identified on ClinicalTrials.gov and in the Chinese Clinical Trial Registry. The two most informative articles were respectively a meta-analysis and a pharmacovigilance study on registry. Bitta et al. (2017) conducted a meta-analysis on antimalaria-drugs with a total of 51 studies involving 205,175. For chloroquine, the median overall prevalence of PAE in prophylaxis studies was 7.1 (95 %CI) and 4.9 in malaria studies 4.9 (95 %CI).

In a recent real-world study using the FDA Adverse Event (AE) Reporting System authors (Sato et al., 2020) conducted an analysis for the detection of PAE signals associated with the use of chloroquine (or...
HCQ). There were 4336 case reports with exposure to chloroquine, of which 520 (12.0 %) reported PAEs. Exposure to chloroquine was associated with a statistically significant high reporting of amnesia, delirium, hallucinations, depression, and loss of consciousness. Their results did not suggest a potential link between the use of chloroquine and an increased risk of suicide. There are numbers of confounding factors in evaluating PAE risk such as the Malaria or other medical conditions effects versus drug effects in patients, the prophylaxis versus treatment and the underlying neuropsychiatric risk. We can predict that it will be the same limitation with COVID-19 in the future studies since COVID pandemic per se is linked to psychological and social distress (Rajkumar, 2020; Tandon, 2020). Currently, at least 80 trials of chloroquine, HCQ, or both, sometimes in combination with other drugs, are registered worldwide for the coronavirus. An ongoing severe pandemic may warrant flexibility in the interpretation of evidence in the interest of public health. We are still waiting for a systematic review using standard Cochrane methods that provides summary estimates of effects for both treatment and prophylactic use of chloroquine and HCQ, including PAE in the safety section of the reports (Fihn 2020, Singh et al., 2020). Because of her previous history of psychosis, we are not sure that we would recommend prophylaxis with HCQ for the nurse patient. It would be interesting to have the opinion of our esteemed colleagues in India. The global health model is largely based on technical assistance and the ability to communicate from the United States, and other wealthy countries, whose response has been delayed at best (The Lancet Global Health, 2020). Medical recommendations must come from all over the world.

### Table 1

| Psychiatric presentation | Medical condition | Authors (Alphabetical order) | Year |
|--------------------------|-------------------|------------------------------|------|
| Manic episode            | Lupus             | Rab SM. Two cases of chloroquine psychosis. BMJ. 1962;1:1275. | 1962 |
|                          |                   | Rao GL., Wilson R., Li F, Spassoff R., Bigrelow G., Spiner N. | 1963 |
|                          |                   | Psychotic symptoms in individuals serving overseas. Lancet. 1985;2:37. | 1985 |
|                          |                   | doi: 10.1016/S0140-6736(85)90078-9. | |
|                          |                   | Insomnia induced by chloroquine in the treatment of lupus erythematosus disseminatus. Presse Med. 1991;20:659. | 1991 |
|                          |                   | Reis J. | 1991 |
|                          |                   | Psychosis, Mood | 1990 |
|                          |                   | Rockwell DA. Psychiatric complications with chloroquine and quinacrine. Am J Psychiatry 1968; 124 : 1257 – 60. | 1968 |
|                          |                   | Saboh S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. Am J Ther. 2007;14:406-407. | 2007 |
|                          |                   | doi: 10.1097/MJT.0b013e1820e4b0e. | |
|                          |                   | Psychosis, Mood | 1964 |
|                          |                   | Sapp OL. Toxic psychosis due to quinacrine and chloroquine. JAMA. 1964;187:373–375. doi: 10.1001/jama.1964.03660180050208. | 1964 |
|                          |                   | Malaria | 2005 |
|                          |                   | Telge DS, van der Vl AJ, Schmmer B, Droogleever-Fortuy HA, Saurerwein RW. Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann Pharmacother. 2005;39:551–554. doi: 10.1345/aph.1E409. | 2005 |
|                          |                   | Seizures | 1968 |
|                          |                   | Torrey EF. Chloroquine seizures. Report of four cases. JAMA 1968; 204 : 867 – 70. | 1968 |
|                          |                   | Psychosis, Mood | 2006 |
|                          |                   | Tran TM, Browning J, Dell ML. Psychosis with paranoid delusions after a therapeutic dose of melflufen: a case report. | 2006 |
|                          |                   | Psychosis, Malaria | 1985 |
|                          |                   | Ward WQ, Walter-Ryan WG, Shehi GM. Toxic psychosis : a complication of antimarial therapy. J Am Acad Dermatol 1985; 12 : 863 – 5. | 1985 |
Declaration of Competing Interest

The authors declare no conflict of interest.

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Bitta, M.A., Karuki, S.M., Mweka, C., Gwer, S., Mwai, L., Newton, C.R.J.C., 2017. Antimalarial drugs and the prevalence and mental and neurological manifestations: a systematic review and meta-analysis. Wellcome Open Res. 2, 13. https://doi.org/10.12688/wellcomeopenres.10658.2. Published 2017 Jan 2.

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Corregiani, A., Ingoglia, G., Ippolito M Giarratano, A., Einav, S., 2020. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J. Crit. Care. https://doi.org/10.1016/j.jccr.2020.03.005. (published online March 10).

Duparc, S., Chalon, S., Miller, S., et al., 2020. Neurological and psychiatric safety of tafenoquine in Plasmodium vivax relapse prevention: a review. Malar. J. 111.

Frimpong, A., Thiam, L.G., Arko-Boham, B., et al., 2018. Safety and e-...