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

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 advisers 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 arhythmias. 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 India. The NGO informed her that the Indian Council of Medical Research has recommended chemoprophylaxis with HCQ (400 mg twice on day 1, then 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 reports a psychotic episode 2 years ago after having stayed in Haiti for 3 weeks. She had started on chloroquine antimalarial chemoprophylaxis - 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 recorded 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 tachypsychia, 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 prophylaxy for the COVID-19 (Mitjà 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

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Table 1
Alphabetical directory of case reports related to neuropsychiatric deleterious effect of chloroquine or hydroxychloroquine.

Psychiatric presentation	Medical condition	Authors (Alpahabetic order)	Year
Manic episode		Akhtar S, Mukherjee S. Chloroquine induced mania. Int J Psychiatry Med 1993; 23: 349 – 56.	1993
Capgras Syndrome		Bhatia MS, Singhal PK, Agrawal P, Malik SC. Capgras syndrome in chloroquine induced psychosis. Indian J Psychiatry. 1988;30:311–313.	1988
Psychosis		Bhatia MS. Chloroquine—induced recurrent psychosis. Indian J Med Sci. 1996;50:302–304.	1996
Psychosis		Biswas PS, Sen D, Majumdar R. Psychosis following chloroquine ingestion: a 10-year comparative study from a malaria-hyperendemic district of India. Gen Hosp Psychiatry. 2014;36:181–186. doi: 10.1016/j.genhosppsych.2013.07.012	2014
Bipolar dosrder Manic Episode	Lupus	Bogaczewicz J, Sobow T, Bogaczewicz A, Robak E, Bienkowski P, Sysa-Jedrzejowska A, et al. Exacerbations of bipolar disorder triggered by chloroquine in systemic lupus erythematosus—a case report. Lupus. 2014;23:188–193. doi: 10.1177/0961203313513818.	2014
Psychosis		Brookes DB. Chloroquine psychosis. BMJ. 1966;1:983. doi: 10.1136/bmj.1.5493.983	1966
Psychosis		Collins GB, McAllister MS. Chloroquine psychosis masquerading as PCP: a case report. J Psychoactive Drugs. 2008;40:211–214. doi: 10.1080/02791072.2008.10400633.	2008
Amnesia		Cras P, Martin JJ. Transient global amnesia following ingestion of chloroquine. J Neurol Neurosurg Psychiatry. 1990;53:926. doi: 10.1136/jnnp.53.10.926.	1990
Psychosis	Chronic Q fever	Das P, Rai A, Chopra A, Philbrick K. Psychosis likely induced by hydropxychloroquine in a patient with chronic Q fever: a case report and clinically relevant review of pharmacology. Psychosomatics. 2014;55:409–413. doi: 10.1016/j.psym.2013.06.017.	2014
Psychosis	Lupus	Evans RL, Khalid S, Kinney JL. Antimalarial psychosis revisited. Arch Dermatol 1984; 120 : 765 – 7.	1984
Psychosis		Garg P, Mody P, Lall KB. Toxic psychosis due to chloroquine. Indian J Pediatr. 1990;57:133–134. doi: 10.1007/BF02722148.	1990
Psychosis, mood	Lupus	Gonzales-Nieto JA, Costa-Juan E. Psychiatric symptoms induced by hydroxychloroquine. Lupus. 2015;24:339–340. doi: 10.1177/0,961,203,314,558,863	2015
Suicide behavior		Good MI, Shader RI. Behavorial toxicity and equivocal suicide associated with chloroquine and its derivatives. Am J Psychiatry 1977 ; 134 : 798 – 801.	1977
Psychosis	Lupus	Hsu WH, Chiu NY, Huang SS. Hydroxychloroquine-induced acute psychosis in a systemic lupus erythematosus female. Acta Neuropsychiatrica. 2011;23:318–319. doi: 10.1111/j.1601 – 5215.2011.00575.x.	2011
Psychosis Suicidal behavior		Jousset N, Rougé-Maillart C, Turcant A, Guilleux M, Le Bouil A, Tracqui A. Suicide by skull stab wounds: a case of drug-induced psychosis. Am J Forensic Med Pathol. 2010;31:378–381. doi: 10.1097/PAF.0b013e3181f9443c	2010
Psychosis		Kwak YT, Yang Y, Park SY. Chloroquine-associated psychosis mimicking very late-onset schizophrenia: case report. Geriatr Gerontol. 2015;15:1096–1097. doi: 10.1111/ggi.12490	2015
Manic episode		Lovestone S. Chloroquine-induced mania. Br J Psychiatry 1991; 159: 164 – 5.	1991
Psychosis		Masson C, Chéron F, Gautier MS, Cambier J. Psychose aiguë après prise de chloroquine. Presse Med 1990 ; 19 : 334.	1990
Psychosis, mood		Maxwell NM, Nevin RL, Stahl S, et al. Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. Clin Case Rep. 2015;3(6):379–387. doi: 10.1002/ccr3.238	2015
Psychosis		Mohan D, Mohandas E, Rajat R. Chloroquine psychosis: a chemical psychosis? J Natl Med Assoc. 1981;73:1073–1076.	1981
Psychosis		Mustakallio KK, Pihkanen TA, Putkonen T. Toxic psychosis during chloroquine treatment. Ann Med Intern Fenn. 1962;51:223–228	1962
Psychosis		Rab SM. Two cases of chloroquine psychosis. BMJ. 1963;1:1275. doi: 10.1136/bmj.1.5340.1275.	1963
Psychosis	Malaria prevention	Ragan E, Wilson R, Li F, Spasoff R, Bigelow G, Spinner N. Psychotic symptoms in volunteers serving overseas. Lancet. 1985;2:37. doi: 10.1016/S0140 – 6736(85)90078 – 9.	1985
Insomnia	Lupus	Reis J. Insomnia induced by chloroquine in the treatment of lupus erythematosus disseminatus. Presse Médicale. 1991;20:659	1991
Psychosis, Mood		Rockwell DA. Psychiatric complications with chloroquine and quinacrine. Am J Psychiatry 1968 ; 124 : 1257 – 60.	1968
Psychosis		Sahoo S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. Am J Ther. 2007;14:406–407. doi: 10.1097/MJT.0b013e31802e4b0e.	2007
Psychosis		Sapp OL. Toxic psychosis due to quinacrine and chloroquine. JAMA. 1964;187:373–375. doi: 10.1001/jama.1964.03060180059026.	1964
Psychosis, Mood	Malaria	Telgt DS, van der Ven AJ, Schimmer B, Droogleever-Fortuyn HA, Sauerwein RW. Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann Pharmacother. 2005;39:551–554. doi: 10.1345/aph.1E409.	2005
Seizures		Torrey EF. Chloroquine seizures. Report of four cases. JAMA 1968; 204 : 867 – 70.	1968
Psychosis	Malaria	Tran TM, Browning J, Dell ML. Psychosis with paranoid delusions after a therapeutic dose of mefloquine: a case report. Malaria J. 2006;5:74. doi: 10.1186/1475 – 2875-5 – 74.	2006
Psychosis	Malaria	Ward WQ, Walter-Ryan WG, Shehi GM. Toxic psychosis : a complication of antimalarial therapy. J Am Acad Dermatol 1985; 12 : 863 – 5.	1985

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.

Declaration of Competing Interest

The authors declare no conflict of interest

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