Iran J Psychiatry Behav Sci. 2023 September; 17(3):e119013. https://doi.org/10.5812/ijpbs-119013.

Published online 2023 July 18. **Review Article**

The Ignored Psychiatric Aspect of Chloroquine in the COVID-19 Outbreak Period: A Narrative Review Study

Mahsa Kamali [1], Marzieh Azizi [2] and Forouzan Elyasi [3, 4, *]

[1] Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran
[2] School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[3] Psychiatry and Behavioral Sciences Research Center, Sexual and Reproductive Health Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran
[4] Department of Psychiatry, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[*] *Corresponding author*: Consultation-Liaison Psychiatry Ward, Imam Khomeini General Hospital, Razi Ave., P. O. Box: 48157-33971, Sari, Iran. Tel: +98-1133370885, Fax: +98-1133363754, Email: forouzan.el@gmail.com

Received 2021 August 27; **Revised** 2023 June 26; **Accepted** 2023 June 27.

Abstract

Context: Several studies have shown that chloroquine can effectively diminish the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As such, other studies have also supported this statement, but the psychiatric side effects of chloroquine have not been taken into account.
Objectives: The current study aimed to briefly review and discuss the safety of chloroquine.
Evidence Acquisition: A narrative literature search on databases was carried out on studies without time limitations. A combination of the two main keywords of "Chloroquine" and "Psychiatric Side Effects" was used to search databases. A manual search was performed to find the relevant articles, and finally, 15 studies were reviewed. Data were shown in the table and then summarized by narrative synthesis.
Results: The literature review revealed the pharmaceutical characteristics of chloroquine, the safety of chloroquine, and the management of chloroquine's side effects. Also, the studies showed that chloroquine had psychiatric symptoms varying from insomnia to catatonia, toxic psychosis, and suicidal attempts, as well as behavioral manifestations, including most frequently extreme irritability, restlessness, abusiveness, distractibility, pressured speech, flight of ideas, grandiosity delusion, and auditory and visual hallucinations.
Conclusions: Given the probability of a wide range of possible psychiatric symptoms following chloroquine, physicians should cautiously prescribe antiviral agents, and healthcare workers should also notice any psychiatric symptoms after administrating the chloroquine.

Keywords: Chloroquine, Coronavirus Disease 2019, Infectious Disease, Psychiatric Side Effects

1. Context

The coronavirus disease 2019 (COVID-19) has had numerous side effects on mental health status (1, 2). Several medications have been considered for the treatment of COVID-19. However, the efficacy of these medications is unclear (3-6). In a study, the neuropsychiatric side effects of oseltamivir have been addressed (7). Another medication in this regard is chloroquine, introduced by the World Health Organization (WHO) in 2020 (8) and the Food and Drug Administration (FDA) (9) as an essential medicine for the prevention and treatment of COVID-19 pneumonia (8-12). Numerous articles have been published at the same time since the start of the COVID-19 outbreak. These studies have demonstrated that chloroquine could effectively diminish the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As such, other studies have also supported this statement (11-14), but the psychiatric side effects of chloroquine have not been taken into account. Chloroquine phosphate administration for COVID-19 patients has been highlighted in the first version of the flowchart published on February 27, 2020, by the Ministry of Health and Medical Education in Iran. The protocol of chloroquine was a single dose of 500 mg for inpatients and 250 mg for outpatients twice a day for five days. Then, in the sixth version, published on April 29, 2020, the protocol of this medicine for high-risk

individuals and outpatients was 500 mg twice a day on the first day and then 250 mg twice a day for at least five days. It should be noted that this dose of medicine should be continued for up to ten days if the initial symptoms remain. For inpatients, chloroquine can be administered 500 mg twice a day on the first day and then 250 mg twice a day for one to two weeks (15).

2. Objectives

The present study aimed to briefly review and discuss the safety of chloroquine. In fact, we sought to answer the following questions:

- What is the possible mechanism of psychiatric side effects of chloroquine?

- Is chloroquine a safe choice in COVID-19 management?

- What should we do regarding psychiatric side effects following chloroquine treatment?

The results of this narrative review will provide a comprehensive view for healthcare providers on COVID-19 patient management to support them against psychiatric side effects induced by chloroquine.

3. Methods

3.1. Search Strategy

A narrative literature search on the databases of Web of Science (WoS), Scopus, PubMed, and Google Scholar was carried out on studies without time limitations. The search strategy consisted of combining MeSH terms and keywords of chloroquine toxicity, psychiatry, delusion, psychotic disorder, and depression. A manual search was also performed to find the relevant articles.

3.2. Inclusion Criteria

The inclusion criteria included the English and Persian language case reports containing relevant data to this review.

3.3. Exclusion Criteria

Exclusion criteria included the lack of access to the full texts of articles.

3.4. Selection Strategy

Two authors (M. K. and M. A.) performed the literature search and reviewed the titles and abstracts of the articles independently. Then, the articles were assessed based on the inclusion and exclusion criteria, and disagreements were solved by a psychiatrist (F. E.). Also, the critical opinion of the psychiatrist (F. E.) was used in all stages of the review process.

3.5. Data Extraction

Data were extracted in the table containing the age of patients, a history of psychiatric disorders, the dose of chloroquine administration, other concomitant medications, comorbidities, psychiatric side effects, and treatment by narrative synthesis.

4. Results

Search in databases resulted in retrieving 280 articles. After removing 100 duplicated articles, 180 studies were screened using titles and abstracts. Then, review studies (46), letters to the editor/commentaries (25), and clinical trials (94) were excluded. Finally, 15 articles were reviewed (Table 1).

4.1. Pharmaceutical Characteristics of Chloroquine

Considering the pharmacokinetics of chloroquine, this medicine has a cumulative feature in the body with a long-term plasma half-life whose concentration in plasma is not an appropriate predictor of brain concentration, estimated to be 10-30 times higher than plasma (19). This high concentration may lead to adverse drug events (ADEs) such as psychiatric symptoms varying from insomnia (29) to catatonia (30), toxic psychosis (31, 32), suicidal attempts (33), as well as behavioral manifestations including most frequently extreme irritability, restlessness, abusiveness, distractibility, pressured speech, flight of ideas, grandiosity delusion, and auditory and visual hallucinations (34). It should be emphasized that the neuropsychiatric side effects of chloroquine may emerge even in cases receiving therapeutic doses. However, acute psychosis has occurred at high doses (2 - 6 g/day) (35, 36) and therapeutic antimalarial doses (total dose of 1500 mg) (19, 37).

The accurate mechanism of psychiatric manifestations by this drug has still remained unknown. Various hypothesized mechanisms have been reported. Chloroquine acts as a muscarinic antagonist, and a chloroquine-muscarinic cholinergic system interaction has been reported (33). It is supposed that neurotransmitter systems such as polyamines (particularly spermidine), imbalances in acetylcholine, and prostaglandin E-antagonist activity may play the main roles in its mechanism (33). Also, chloroquine acts as N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), and dopamine-serotonin antagonist (38, 39). According to the related literature, chloroquine might induce imbalances in cholinergic receptors (40) and initiate glucose-6-phosphate dehydrogenase (G6PD) deficiency (41). All these neurotransmitters play

major roles in cognition, perception, and mood pathway. Therefore, they may provoke psychiatric symptoms (42). On the other hand, chloroquine may cause cell death (43). A possible mechanism is the relationship between chloroquine and altered gene expression in cell death pathways, including inhibition of poly (ADP-ribose) polymerase (PARP1) and PARP2, as well as metabolomics perturbations that lead to failure in nicotinamide adenine dinucleotide (NAD^+) balance and aspartate availability (44). Also, encephalopathy and psychiatric symptoms may occur following inflammatory responses to influenza (45). Of course, COVID-19 patients may present neuropsychiatric symptoms, and chloroquine may aggravate or initiate the neuropsychiatric symptoms (46). It is supposed that behavioral symptoms, hallucinations, delirium, or abnormal behaviors arise in patients with encephalitis or encephalopathy. In addition, patients infected with influenza may manifest psychiatric symptoms attributable to immunological reactions rather than virus effectiveness on the central nervous system (CNS) (47). In addition, chloroquine affects the lipid bilayer membranes and interacts with lysosomal activity. Also, it prevents the expression of pro-inflammatory cytokines via toll-like receptor (TLR) activation (48). They lead to CNS toxicity which may appear with nausea, vomiting, dizziness, headache, and delirium (49).

4.2. The Safety of Chloroquine

According to the results of several studies, extensive psychiatric manifestations have been reported following chloroquine use (16-22, 24, 26-28, 50, 51) (Table 1). Chloroquine has a narrow therapeutic window, and CNS toxicity and neuropsychiatric symptoms may occur at therapeutic doses (19, 27). However, 10 - 35% of mortality cases have occurred in overdose conditions (46). Based on the results of a study in 2014, 76.2% of psychiatric symptoms were mood disorders. The results of this study demonstrated no significant relationship between the prescribed dose of chloroquine and the severity of psychosis. In this study, the group with psychosis following chloroquine (i.e., the PFC group) exposure was compared with equal-age patients suffering from brief psychotic disorders (i.e., the BPD group). The findings of this study revealed that the PFC group had an early manifestation of psychosis, including mixed affective psychosis, higher levels of restlessness, irritability, agitation, and more disturbed thought content and orientation but better insight compared with the BPD group. Also, the patients in the PFC group showed prominent positive symptoms with visual hallucinations and de-realization experiences (43).

Another case report with the regime of chloroquine due to malaria revealed that all disease symptoms were alleviated on the third day of therapy, but the patient manifested hyperactivity, excessive talking, argumentativeness, extreme irritability, grandiosity, abusiveness, and lack of sleep. According to the history of manic episodes three years ago, the patient was prescribed haloperidol 20 mg daily, and the manic symptoms were remitted within two weeks. The patient continued that treatment for at least three months and then ceased on his own (52). Another case with manic manifestations has been reported who was treated with chloroquine 250 mg per day. One month later, other psychiatric symptoms such as anxiety, flight of ideas, attention deficit disorder (20), delusions of grandeur, distractibility, and an overflow of energy appeared (51). In another case report with the diagnosis of systemic lupus erythematosus (SLE), chloroquine was administered for three episodes of the disease. In two episodes, the patient's symptoms were relieved without any manifestations of psychiatric symptoms; however, the patient showed symptoms of severe depression, including low mood, psychomotor retardation, feelings of pessimism and worthlessness, loss of interest, excitation, and suicidal thoughts in the first prescription of chloroquine in the third episode. It should be noted that this patient had a history of bipolar disorder (24).

4.3. Management of Chloroquine Side Effects

Once psychiatric side effects of chloroquine appear, the best treatment choice is to discontinue chloroquine if possible and prescribe specific medications according to the clinical manifestations of the psychiatric disorders (38). In this regard, a study reported that a sub-acute paranoid-like disorder was resolved two days after chloroquine discontinuation (50). Psychiatric manifestations usually occur from one to two weeks with chloroquine treatment, and symptoms are commonly resolved within several days following discontinuation of this agent and prescription of psychiatric treatment. It should be reminded that other diagnoses of psychiatric complications following chloroquine use, including comorbidities such as metabolic disorders, primary psychiatric disorders, influenza virus-associated encephalopathy, glucocorticoid-induced psychotic disorders, and other antiretroviral psychiatric side effects, should be ruled out (38).

5. Discussion

The present study aimed to briefly review and discuss the safety of chloroquine and subsequent psychiatric

side effects. The results showed that chloroquine had been prescribed in patients following malaria (7 studies), COVID-19 (3 studies), SLE (2 studies), rheumatoid arthritis (2 studies), and amoebic liver abscess (1 study). Chloroquine as an antimalarial agent was discovered by Bayer A.G. in Germany in 1934 (53). Chloroquine inhibits the polymerization and detoxification of hematin. So, the accumulation of free hematin that is highly toxic to Plasmodium contributes to the dissolution of the cell membrane and, finally, the death of the parasites (54, 55). Therefore, chloroquine has been used as an effective antimalarial management for decades (56). Another indication of chloroquine is in the treatment of inflammatory rheumatic diseases such as SLE and rheumatoid arthritis (57, 58). Chloroquine has direct immunomodulatory effects, so it can protect patients against infections following inflammatory rheumatic diseases (59). The new indication of chloroquine, COVID-19 management, was controversial. Multiple theories have been proposed, including increasing the endosomal pH level and its essential role in the division of SARS-CoV-2 spike proteins, inhibiting quinine reductase-2, and then reducing the sialic acid synthesis (60, 61).

The literature review showed that most patients were 25-46-year-old. A clinical trial reported the mean age of patients who received 300 mg chloroquine over a 12-weeks period to be 25.7 years and showed CNS complications (62). In another study, the mean age of patients with post-chloroquine psychosis was shown to be 31 years (43). The present review revealed that most patients were female (10 cases). This finding was also obtained in another review study investigating the neuropsychiatric side effects of chloroquine (63). The results of the current literature review showed that most patients had no family or personal history of psychiatric disorders, although the risk of psychiatric events may be influenced by familial risk (64). It can be a practical warning notice for healthcare providers that expect psychiatric manifestations following chloroquine therapy in patients with no previous history. The present case review revealed the psychiatric side effects that may be observed in the therapeutic dose of chloroquine. This issue should be considered a clinical notice to frequently assess psychiatric symptoms.

The present narrative review reported a wide range of chloroquine-to-side effects times, ranging from two days to three months following chloroquine administration. It can be due to the slow terminal half-life of the plasma concentration concerning time, approximately 3 - 5 days, after a single dose of 300 mg chloroquine (65). The results of a study revealed that most side effects following chloroquine administration were observed between 0.2 and 0.4 μg/mL. So, we can consider this criterion regarding the psychiatric side effects of chloroquine (66). In the cases reported in our study, the dose was wide-ranging, from 125 mg to 1800 mg. Unfortunately, the frequency of medication was unknown.

The most commonly reported psychiatric side effects were mood disorders, psychosis, and insomnia. The results of a study revealed that 76.2% of psychiatric symptoms following chloroquine administration were mood disorders (43). A multi-transmitter hypothesis of chloroquine-induced psychiatric disorders has been proposed considering central dopamine, glutamate, and acetylcholine pathways involved in psychosis and depression (67).

In all cases of the current literature review, symptomatic therapy, including heterocyclic antidepressants (amitriptyline and mirtazapine), selective serotonin reuptake inhibitors (SSRIs), sertraline, phenothiazine (chlorpromazine), benzodiazepine (oxazepam, diazepam, and lorazepam), antipsychotic agents (haloperidol, olanzapine, risperidone, amisulpride, and perazine), antihistamines (hydroxyzine), and corticosteroids (methylprednisolone) treatment, were used. Side effect management is important to avoid abandoning treatment (68).

5.1. Conclusions

Given the probability of a wide range of unknown interactions and mechanisms due to the co-administration of antiretroviral and other drugs, physicians should cautiously choose antiviral agents. Considering the large number of patients with COVID-19 receiving chloroquine as a part of their therapeutic plan, psychiatrists and other healthcare professionals need to reflect on the adverse effects of chloroquine administration on patients' mental health status.

Acknowledgments

We would like to thank the Mazandaran University of Medical Sciences for providing the research environment.

Footnotes

Authors' Contribution: F. E.: Study design, final manuscript edition, and critical revision; M. K. and M. A.: Conducting the study and writing the initial draft. All authors read and approved the final manuscript.

Conflict of Interests: The authors declared no conflict of interest.

Funding/Support: This research received no funding.

References

1. Azizi M, Kamali M, Moosazadeh M, Aarabi M, Ghasemian R, Hasannezhad Reskati M, et al. Assessing mental health status among Iranian healthcare workers in times of the COVID-19 pandemic: A web-based cross-sectional study. *Brain Behav*. 2021;**11**(8):e2304. [PubMed ID: 34333852]. [PubMed Central ID: PMC8413818]. https://doi.org/10.1002/brb3.2304.
2. Kamali M, Moosazadeh M, Azizi M, Ghasemian R, Hasannezad Reskati M, Elyasi F. Anxiety due to COVID-19 among healthcare providers during pandemic: A web-based cross-sectional survey in Iran. *Neuropsychopharmacol Rep*. 2021;**41**(4):496–510. [PubMed ID: 34647435]. [PubMed Central ID: PMC8646633]. https://doi.org/10.1002/npr2.12213.
3. Weng C, Xie R, Han G, Yuan Y, Li S, Wang C, et al. Safety and Efficacy of Paxlovid Against Omicron Variants of Coronavirus Disease 2019 in Elderly Patients. *Infect Dis Ther*. 2023;**12**(2):649–62. [PubMed ID: 36696068]. [PubMed Central ID: PMC9875765]. https://doi.org/10.1007/s40121-023-00760-x.
4. Amani B, Amani B. Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: A rapid review and meta-analysis. *J Med Virol*. 2023;**95**(2):e28441. [PubMed ID: 36576379]. [PubMed Central ID: PMC9880713]. https://doi.org/10.1002/jmv.28441.
5. Nhean S, Varela ME, Nguyen YN, Juarez A, Huynh T, Udeh D, et al. COVID-19: A Review of Potential Treatments (Corticosteroids, Remdesivir, Tocilizumab, Bamlanivimab/Etesevimab, and Casirivimab/Imdevimab) and Pharmacological Considerations. *J Pharm Pract*. 2023;**36**(2):407–17. [PubMed ID: 34597525]. [PubMed Central ID: PMC10064180]. https://doi.org/10.1177/08971900211048139.
6. Bakheit AH, Darwish H, Darwish IA, Al-Ghusn AI. Remdesivir. In: Al-Majed AA, editor. *Profiles of Drug Substances, Excipients and Related Methodology*. **Vol. 48**. Cambridge, MA: Academic Press; 2023. p. 71–108.
7. Ghafour I, Elyasi F. The Neuropsychiatric Side Effects of Oseltamivir, an Early Solution in the Coronavirus. *Pharm Biomed Res*. 2020;**6**(s2):61–4. https://doi.org/10.18502/pbr.v6i(S2).5654.
8. World Health Organization. *Informal consultation on the dose of chloroquine and hydroxychloroquine for the SOLIDARITY Clinical Trial*. 2020. Available from: https://www.who.int/docs/default-source/documents/r-d-blueprint-meetings/rd-blueprint-expert-group-on-cq-dose-call-apr8.pdf.
9. US Food and Drug Administration. *Coronavirus Disease 2019 (COVID-19)*. 2020. Available from: https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19.
10. Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Res*. 2013;**23**(2):300–2. [PubMed ID: 23208422]. [PubMed Central ID: PMC3567830]. https://doi.org/10.1038/cr.2012.165.
11. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;**14**(1):72–3. [PubMed ID: 32074550]. https://doi.org/10.5582/bst.2020.01047.
12. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;**55**(3):105923. [PubMed ID: 32070753]. [PubMed Central ID: PMC7134866]. https://doi.org/10.1016/j.ijantimicag.2020.105923.
13. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis*. 2003;**3**(11):722–7. [PubMed ID: 14592603]. [PubMed Central ID: PMC7128816]. https://doi.org/10.1016/s1473-3099(03)00806-5.
14. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;**30**(3):269–71. [PubMed ID: 32020029]. [PubMed Central ID: PMC7054408]. https://doi.org/10.1038/s41422-020-0282-0.
15. Ministry of Health and Medical Education of the Islamic Republic of Iran. *[About COVID-19]*. 2020. Persian. Available from: http://medcare.behdasht.gov.ir/index.aspx?siteid=312&fkeyid=&siteid=312&pageid=61966.
16. Das EM, Mohan D. Chloroquine-related depression. *Indian J Psychiatry*. 1981;**23**(2):184–5. [PubMed ID: 22065137]. [PubMed Central ID: PMC3013174].
17. Bhatia MS, Singhal PK, Agrawal P, Malik SC. Capgras syndrome in chloroquine induced psychosis. *Indian J Psychiatry*. 1988;**30**(3):311–3. [PubMed ID: 21927327]. [PubMed Central ID: PMC3010609].
18. Lovestone S. Chloroquine-induced mania. *Br J Psychiatry*. 1991;**159**:164–5. [PubMed ID: 1888972]. https://doi.org/10.1192/bjp.159.1.164b.
19. 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**(3):551–4. [PubMed ID: 15728331]. https://doi.org/10.1345/aph.1E409.
20. Sahoo S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. *Am J Ther*. 2007;**14**(4):406–7. [PubMed ID: 17667217]. https://doi.org/10.1097/MJT.0b013e31802e4b0e.
21. Zaki SA, Mauskar A, Shanbag P. Toxic psychosis due to chloroquine overdose: a case report. *J Vector Borne Dis*. 2009;**46**(1):81–2. [PubMed ID: 19326713].
22. Gulec G, Yenilmez C, Ayranci U. Sulfasalazine plus Chloroquine-Induced Mood Disorder in a Patient with Rheumatoid Arthritis. *Iran J Med Sci*. 2009;**34**(1):72–5.
23. Plesnicar B, Velikonja I, Plesnicar A, Vitorovic S. Two Challenge and Rechallenge Episodes of Chloroquine-Induced Psychotic Mania in a Patient with Rheumatoid Arthritis. *Aktuelle Rheumatol*. 2013;**38**(3):177–9. https://doi.org/10.1055/s-0032-1327626.
24. 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**(2):188–93. [PubMed ID: 24297641]. https://doi.org/10.1177/0961203313513818.
25. Anonymous. Chloroquine: Subacute paranoid-like disorder: case report. *Reactions Weekly*. 2016;**1632**(1):85. https://doi.org/10.1007/s40278-016-24048-5.
26. Choughule A, Salunkhe R. Chloroquine induced psychosis in an adult patient with amoebic liver abscess: A case report. *Indian J Ment Health*. 2019;**6**(1):115–8.
27. Emmanuel S, Ostlundh L. Psychiatric adverse events with hydroxychloroquine during COVID-19 pandemic. *Asian J Psychiatr*. 2020;**54**:102203. [PubMed ID: 32603983]. [PubMed Central ID: PMC7305495]. https://doi.org/10.1016/j.ajp.2020.102203.
28. Benjelloun R, Otheman Y, El Kettani C. Psychiatric side effects of chloroquine in COVID-19 patients: two case reports. *Pan Afr Med J*. 2020;**35**(Suppl 2):83. [PubMed ID: 33623607]. [PubMed Central ID: PMC7875809]. https://doi.org/10.11604/pamj.supp.2020.35.24064.
29. Reis J. [Insomnia induced by chloroquine in the treatment of lupus erythematosus disseminatus]. *Presse Med*. 1991;**20**(14):659. French. [PubMed ID: 1828574].
30. Akhtar S, Mukherjee S. Chloroquine induced mania. *Int J Psychiatry Med*. 1993;**23**(4):349–56. [PubMed ID: 8175247]. https://doi.org/10.2190/8DRE-DBNH-MXXG-7AJF.
31. Rab SM. Two cases of chloroquine psychosis. *Br Med J*. 1963;**1**(5340):1275. [PubMed ID: 13972819]. [PubMed Central ID: PMC2123312]. https://doi.org/10.1136/bmj.1.5340.1275.
32. Sapp III OL. Toxic Psychosis Due to Quinarcrine and Chloroquine. *JAMA*. 1964;**187**:373–5. [PubMed ID: 14085046]. https://doi.org/10.1001/jama.1964.03060180059026.
33. Good MI, Shader RI. Behavioral toxicity and equivocal suicide associated with chloroquine and its derivatives.

Am J Psychiatry. 1977;**134**(7):798–601. [PubMed ID: 326063]. https://doi.org/10.1176/ajp.134.7.798.
34. Brookes DB. Chloroquine psychosis. *Br Med J*. 1966;**1**(5493):983. [PubMed ID: 20836225]. [PubMed Central ID: PMC1844857]. https://doi.org/10.1136/bmj.1.5493.983.
35. Bhatia MS. Chloroquine–induced recurrent psychosis (brief report). *Indian J Med Sci*. 1996;**50**(11):302–4. [PubMed ID: 9141350].
36. Garg P, Mody P, Lall KB. Toxic psychosis due to chloroquine. *Indian J Pediatr*. 1990;**57**(1):133–4. [PubMed ID: 2361706]. https://doi.org/10.1007/BF02722148.
37. Aneja J, Goya D, Choudhary B. Psychosis consequent to antimalarial drug use in a young child. *J Family Med Prim Care*. 2019;**8**(5):1781–3. [PubMed ID: 31198757]. [PubMed Central ID: PMC6559057]. https://doi.org/10.4103/jfmpc.jfmpc_225_19.
38. Bogaczewicz A, Sobów T. Psychiatric adverse effects of chloroquine. *Psychiatr Psychol Klin*. 2017;**17**(2):111–4. https://doi.org/10.15557/PiPK.2017.0012.
39. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. *Curr Med Chem*. 2001;**8**(4):371–84. [PubMed ID: 11172695]. https://doi.org/10.2174/0929867013373435.
40. Davis KL, Berger PA. Pharmacological investigations of the cholinergic imbalance hypotheses of movement disorders and psychosis. *Biol Psychiatry*. 1978;**13**(1):23–49. [PubMed ID: 146524].
41. Lindenmayer JP, Vargas P. Toxic psychosis following use of quinacrine. *J Clin Psychiatry*. 1981;**42**(4):162–4. [PubMed ID: 7204361].
42. Kehr J, Yoshitake T, Ichinose F, Yoshitake S, Kiss B, Gyertyan I, et al. Effects of cariprazine on extracellular levels of glutamate, GABA, dopamine, noradrenaline and serotonin in the medial prefrontal cortex in the rat phencyclidine model of schizophrenia studied by microdialysis and simultaneous recordings of locomotor activity. *Psychopharmacology (Berl)*. 2018;**235**(5):1593–607. [PubMed ID: 29637288]. [PubMed Central ID: PMC5920013]. https://doi.org/10.1007/s00213-018-4874-z.
43. 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**(2):181–6. [PubMed ID: 24290896]. https://doi.org/10.1016/j.genhosppsych.2013.07.012.
44. Eloranta K, Cairo S, Liljestrom E, Soini T, Kyronlahti A, Judde JG, et al. Chloroquine Triggers Cell Death and Inhibits PARPs in Cell Models of Aggressive Hepatoblastoma. *Front Oncol*. 2020;**10**:1138. [PubMed ID: 32766148]. [PubMed Central ID: PMC7379510]. https://doi.org/10.3389/fonc.2020.01138.
45. Toovey S, Prinssen EP, Rayner CR, Thakrar BT, Dutkowski R, Koerner A, et al. Post-marketing assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: an updated review. *Adv Ther*. 2012;**29**(10):826–48. [PubMed ID: 23054689]. https://doi.org/10.1007/s12325-012-0050-8.
46. Hamm BS, Rosenthal LJ. Psychiatric Aspects of Chloroquine and Hydroxychloroquine Treatment in the Wake of Coronavirus Disease-2019: Psychopharmacological Interactions and Neuropsychiatric Sequelae. *Psychosomatics*. 2020;**61**(6):597–606. [PubMed ID: 32800347]. [PubMed Central ID: PMC7341047]. https://doi.org/10.1016/j.psym.2020.06.022.
47. Chung S, Joung YS. Oseltamivir (tamiflu) induced depressive episode in a female adolescent. *Psychiatry Investig*. 2010;**7**(4):302–4. [PubMed ID: 21253416]. [PubMed Central ID: PMC3022319]. https://doi.org/10.4306/pi.2010.7.4.302.
48. Pedrioli G, Patani R, Paganetti P. Chloroquine, the Coronavirus Crisis, and Neurodegeneration: A Perspective. *Front Neurol*. 2020;**11**:596528. [PubMed ID: 33281734]. [PubMed Central ID: PMC7691290]. https://doi.org/10.3389/fneur.2020.596528.
49. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? *Drug Saf*. 1995;**12**(6):370–83. [PubMed ID: 8527012]. https://doi.org/10.2165/00002018-199512060-00003.
50. Bogaczewicz A, Sobow T, Bogaczewicz J, Bienkowski P, Kowalski J, Wozniacka A. Chloroquine-induced subacute paranoid-like disorder as a complication of dermatological treatment. *Int J Dermatol*. 2016;**55**(12):1378–80. [PubMed ID: 26967266]. https://doi.org/10.1111/ijd.13266.
51. Anonymous. Chloroquine: Psychotic mania in an elderly patient: case report. *Reactions Weekly*. 2013;**1465**(1):14. https://doi.org/10.1007/s40278-013-5168-1.
52. Bhatia MS, Jhanjee A, Oberoi A. A case of chloroquine-induced recurrent mania. *Prim Care Companion CNS Disord*. 2012;**14**(3):PCC.11l01302. [PubMed ID: 23106017]. [PubMed Central ID: PMC3466026]. https://doi.org/10.4088/PCC.11l01302.
53. Mushtaque M; Shahjahan. Reemergence of chloroquine (CQ) analogs as multi-targeting antimalarial agents: a review. *Eur J Med Chem*. 2015;**90**:280–95. [PubMed ID: 25461328]. https://doi.org/10.1016/j.ejmech.2014.11.022.
54. Skrzypek R, Callaghan R. The "pushmi-pullyu" of resistance to chloroquine in malaria. *Essays Biochem*. 2017;**61**(1):167–75. [PubMed ID: 28258239]. https://doi.org/10.1042/EBC20160060.
55. Zhou W, Wang H, Yang Y, Chen ZS, Zou C, Zhang J. Chloroquine against malaria, cancers and viral diseases. *Drug Discov Today*. 2020;**25**(11):2012–22. [PubMed ID: 32947043]. [PubMed Central ID: PMC7492153]. https://doi.org/10.1016/j.drudis.2020.09.010.
56. Commons RJ, Simpson JA, Thriemer K, Humphreys GS, Abreha T, Alemu SG, et al. The effect of chloroquine dose and primaquine on Plasmodium vivax recurrence: a WorldWide Antimalarial Resistance Network systematic review and individual patient pooled meta-analysis. *Lancet Infect Dis*. 2018;**18**(9):1025–34. [PubMed ID: 30033231]. [PubMed Central ID: PMC6105624]. https://doi.org/10.1016/S1473-3099(18)30348-7.
57. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;**73**(3):492–509. [PubMed ID: 24161836]. [PubMed Central ID: PMC3933074]. https://doi.org/10.1136/annrheumdis-2013-204573.
58. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;**78**(6):736–45. [PubMed ID: 30926722]. https://doi.org/10.1136/annrheumdis-2019-215089.
59. Rempenault C, Combe B, Barnetche T, Gaujoux-Viala C, Lukas C, Morel J, et al. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2018;**77**(1):98–103. [PubMed ID: 28970215]. https://doi.org/10.1136/annrheumdis-2017-211836.
60. Tripathy S, Dassarma B, Roy S, Chabalala H, Matsabisa MG. A review on possible modes of action of chloroquine/hydroxychloroquine: repurposing against SAR-CoV-2 (COVID-19) pandemic. *Int J Antimicrob Agents*. 2020;**56**(2):106028. [PubMed ID: 32450198]. [PubMed Central ID: PMC7243790]. https://doi.org/10.1016/j.ijantimicag.2020.106028.
61. Zhao MM, Yang WL, Yang FY, Zhang L, Huang WJ, Hou W, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. *Signal Transduct Target Ther*. 2021;**6**(1):134. [PubMed ID: 33774649]. [PubMed Central ID: PMC7997800]. https://doi.org/10.1038/s41392-021-00558-8.
62. Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, et al. Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol*. 1993;**44**(3):257–65. [PubMed ID: 8256107].
63. Talarico F, Chakravarty S, Liu YS, Greenshaw A, Passos IC, Cao B. Psychiatric side effects induced by chloroquine and hydroxychloroquine: a systematic review of case reports and population studies. Preprint. *medRxiv*. Posted online October 7, 2020. https://doi.org/10.1101/2020.10.05.20207423.
64. Diaz-Castro L, Hoffman K, Cabello-Rangel H, Arredondo A,

Herrera-Estrella MA. Family History of Psychiatric Disorders and Clinical Factors Associated With a Schizophrenia Diagnosis. *Inquiry*. 2021;**58**:1–10. [PubMed ID: 34845937]. [PubMed Central ID: PMC8673879]. https://doi.org/10.1177/00469580211060797.

65. McChesney EW, Banks Jr WF, Mcauluff JP. Laboratory Studies of the 4-Aminoquinoline Antimalarials. II. Plasma Levels of Chloroquine and Hydroxychloroquine in Man after Various Oral Dosage Regimens. *Antibiotics & Chemotherapy*. 1962;**12**(9):583–94.
66. Frisk-Holmberg M, Bergkvist Y, Domeij-Nyberg B, Hellstrom L, Jansson F. Chloroquine serum concentration and side effects: evidence for dose-dependent kinetics. *Clin Pharmacol Ther*. 1979;**25**(3):345–50. [PubMed ID: 310749]. https://doi.org/10.1002/cpt1979253345.
67. Schatzberg AF, Nemeroff CB. *The American psychiatric publishing textbook of psychopharmacology*. Arlington, VA: American Psychiatric Publishing; 2009.
68. Maxwell NM, Nevin RL, Stahl S, Block J, Shugarts S, Wu AH, et al. Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. *Clin Case Rep*. 2015;**3**(6):379–87. [PubMed ID: 26185633]. [PubMed Central ID: PMC4498847]. https://doi.org/10.1002/ccr3.238.

Table 1. The Sample Case Report Studies Concerning Psychiatric Side Effects Following Chloroquine Administration

Authors	Year	Patient	A History of Psychiatric Disorders	Dose of Chloroquine Administration	Other Concomitant Medications	Comorbidities	Psychiatric Side Effects	Treatment
Das and Mohan (16)	1981	A 40-year-old woman	Patient (no), family (no)	Chloroquine 1.5 g, frequency (unknown)	None	Malaria	Four days after drug ingestion: Sleeplessness, loss of interest in doing any work, feeling sad, suicidal ideas, weeping spells, impaired insight	Amitriptyline 100 mg per day
Das and Mohan (16)	1981	A 32-year-old woman	Patient (no), family (no)	Chloroquine 1.8 g, frequency (unknown)	None	Malaria	Five days after drug ingestion: Depressive mood, psychomotor retardation, suicidal and paranoid ideas	Tricyclic antidepressant, dose and frequency (unknown)
Bhatia et al. (17)	1988	A 9-year-old girl	Patient (no), family (no)	Chloroquine 0.5 mg followed by 250 mg chloroquine six hours later. On the second day, 125 mg chloroquine was given	None	Malaria	Three days later: Restless, outburst of abusive, violent behavior, irrelevant talks, poor judgment, lack of insight, disorientation to time, mild impairment of recent memory	Chlorpromazine 300 mg daily in divided doses
Lovestone (18)	1991	A 33-year-old man	Patient (no), family (no)	Chloroquine 300 mg weekly	Proguanil 200 mg daily	Antimalarial prophylaxis	The drug onset was unknown: Mildly irritable, overactive, irritable, talkative, experiencing racing thoughts, expressing delusions of reference and grandeur	Single dose of 5 mg haloperidol
Telgt et al. (19)	2005	A 34-year-old woman	Patient (no), family (no)	Chloroquine 600 mg, followed by 3 more doses of 300 mg after 6, 24, and 48 hours (total dose 25 mg/kg).	None	Malaria	After the third dose of chloroquine: Complaining of "losing her mind" and "feeling like a robot." Signs of paranoid delusions suffer repeatedly from vivid and unpleasant dreams, by day 12: The idea that there was a "short circuit" in her head, constant headache photophobia, dizziness, difficulty focusing, out-of-body experience, not able to control her thoughts, a panic-struck preoccupation with "going mad." Memory disturbances, language difficulties, attention deficit, concentrations of chloroquine were in the therapeutic range (20 - 300 μg/L)	Oxazepam 10 mg at bedtime to alleviate insomnia, all complaints gradually subsided over the next 4 months
Sahoo et al. (20)	2007	A 40-year-old man	Patient (no), family (no)	Chloroquine 1.8 g, frequency (unknown)	None	Malaria	Two days after chloroquine administration: Delusions, auditory hallucinations, agitation, hostility, disturbed sleep, disturbed appetite, stereotypic hand and feet movements, rocking of the body hallucinatory behavior, his speech was loud and punctuated with grunting, expressing the fear that he might be killed and that the world is coming to an end	Intravenous diazepam, injectable antipsychotics, then oral antipsychotics

Zaki et al. (21)	2009	A 7-year-old girl	Patient (unknown), family (unknown)	Chloroquine (base: 150 mg) 10 mg/kg followed by 5 mg/kg at 6, 24, and 48 hours. However, as the parents did not understand the dosing schedule, the total dose of chloroquine received by the child was approximately 100 mg/kg of base as against the total therapeutic dose of 25 mg/kg of base.	Paracetamol, dose (unknown)	High-grade fever, chills, vomiting	Excessive talking, restlessness	olanzapine olanzapine 10 mg/day, discharged on the fourth hospital day
Gulec et al. (22)	2009	A 39-year-old woman	Patient (no), family (no)	Chloroquine 250 mg daily	Sulfasalazine 2 g daily	Rheumatoid arthritis	Two months after initiating chloroquine and sulfasalazine: Insomnia, suicidal tendency, increased energy, behavioral changes, auditory hallucinations, grandiose, persecutive and erotomanic type delusions	Risperidone 2 mg daily and quetiapine 200 mg/day
Plesnicar et al. (23)	2013	A 72-year-old man	Patient (no), family (unknown)	Chloroquine 250 mg daily	Etoricoxib, Gliquidone, Candesartan, Diltiazem, dose (unknown)	Diabetes mellitus, seronegative polyarthritis, arterial hypertension, cured prostate cancer	Two weeks after drug administration that aggravated one month later: Anxiety, delusions of grandeur, flight of ideas, overflow of energy, distractibility with attention deficit, talkative, irritable, feeling extremely well, starting chloroquine on the same dose and after three weeks: Talkative, distractible, delusions of grandeur, no need for sleep, irritable, his attention deficit was pretty pronounced	Risperidone 2 mg daily, then 0.5 mg daily in the follow-up visit
Bogaczewicz et al. (24)	2014	A 31-year-old man	Patient (no), family (no)	Chloroquine 250 mg daily	Methylprednisc 12 mg daily	SLE	Three months later: Depressed mood, psychomotor retardation feelings of pessimism, worthlessness, loss of interest, excitation, suicidal thoughts	Perazine 200 mg daily in three divided doses, sertraline 150 mg daily, mirtazapine 15 mg daily, hydroxyzine 25 mg twice a day, methylprednisolone 4 mg daily for 11 months
Anonymous (25)	2016	A 29-year-old woman	Patient (unknown), family (unknown)	Chloroquine 250 mg daily	Topical treatment with clobetasol propionate	SLE	Three days after drug onset: Persecutory delusions, feelings of de-realization, general feelings of paranoia, delusional perceptions, strong anxiety, occasional visual illusions	Only discontinuation of chloroquine
Choughule and Salunkhe (26)	2019	A 32-year-old man	Patient (no), family (unknown)	Chloroquine 600 mg in divided doses	None	Amoebic liver abscess	On the fifth day: Feeling that there is some supernatural power in his room, feeling that became extremely fearful, pleading for the constant company of family members, irrelevant talk, muttering, aggression, suspiciousness, having a firm belief that some supernatural force is going to harm him, fearful mood, perplexed affect, delusion of persecution against unknown forces or people, auditory hallucinations, illusions and visual imagery related to a devil's shadow, impaired personal and social judgment	Olanzapine 10 mg in divided doses for two weeks

Emmanuel and Ostlundh (27)	2020	A 25-year-old woman	Patient (unknown), family (unknown)	Chloroquine 300 mg, frequency (unknown)	None	Coronavirus disease 2019	Thirty days after chloroquine administration: Behavioral problems, agitation, temporal disorientation, tachypsychia, incoherent speech, delusional syndrome, logorrhoea with: Echolalia, insomnia, psychomotor agitation, chloroquine level was found to be 0.5 mg/L.	Olanzapine, dose and frequency (unknown)
Benjelloun et al. (28)	2020	A 35-year-old woman	Patient (no), family (no)	Chloroquine, dose and frequency (unknown)	Azithromycin dose (unknown)	Coronavirus disease 2019	Three days after treatment: Insomnia, recurrent panic attacks with palpitations, the sensation of imminent death feeling of not being able to control her thoughts, depersonalization derealization, persistent sadness with permanent negative thoughts, fear of dying herself and her loved ones	2.5 mg of lorazepam spread over 24 hours, anxiety symptoms disappeared rapidly after interrupting azithromycin-chloroquine
Benjelloun et al. (28)	2020	A 46-year-old man	Patient (mild depressive episode treated with vortioxetine), family (no)	Chloroquine, dose and frequency (unknown)	Azithromycin dose (unknown)	Coronavirus disease 2019	Nine days after treatment: Symptoms of distress and insomnia, visual hallucinations incoherent speech, the outburst of odd behavior, repeated attempts to run away from hospital	Amisulpride 100 mg per day for a week, psychotic symptoms disappeared totally after 48 hours.

Abbreviation: SLE, systemic lupus erythematosus.