Psychiatric Adverse Effects From Hydroxychloroquine Use:

A Systematic Review

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Abstract

Objective: To conduct a systematic review of the available evidence on hydroxychloroquine (HCQ)-induced psychiatric side effects and their management.

Data sources: A literature search was conducted in PubMed, MEDLINE, PsycINFO, and Cochrane collaboration databases from 2000 to 2024 using the keywords "hydroxychloroquine" AND "psychiatry" OR "psychosis" OR "depression" OR "anxiety" OR "bipolar disorder" OR "delirium" OR "psychotic disorders" OR "psychiatric side effects" OR "psychiatric disorders."

Study selection: English-language articles with studies reporting HCQ-induced psychiatric/neuropsychiatric side effects were included. Duplicate records and studies reporting only chloroquine side effects were excluded.

Results: The review included 16 case reports, 8 original articles, and 3 review articles. HCQ was found to trigger symptoms of psychosis, depression, suicidal ideation, mania/hypomania, anxiety, sleep disturbances, and cognitive impairments. The onset of these psychiatric side effects varied, appearing shortly after starting the medication to a more extended period.

Conclusion: Based on the literature, HCQ may be associated with short-term psychiatric adverse effects. A psychiatric consultation for a thorough clinical and risk factor evaluation to differentiate a primary psychiatric disorder from a drug-induced adverse effect would help guide the management. Dosage adjustments, discontinuing HCQ if feasible, and psychotropic medications like olanzapine or risperidone may be necessary when psychiatric side effects are secondary to HCQ. Further studies are needed to validate these findings.

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Hydroxychloroquine (HCQ) is a hydroxide derivative of chloroquine (CQ). It is approved by the US Food and Drug Administration (FDA) for treating malaria, systemic lupus erythematosus (SLE), discoid lupus erythematosus, and rheumatoid arthritis. The off-label uses include Q-fever, porphyria cutanea tarda, primary Sjogren disease, and sarcoidosis.[1–4]

Since CQ and HCQ exhibit similar physiochemical properties, many pharmacokinetic features of HCQ are often inferred from CQ studies,[5] namely, high oral bioavailability, high tissue penetrance, partial hepatic metabolism, and high volumes of distribution (as they diffuse into adipose tissue). However, CQ has diminished recently due to widespread malarial parasite drug resistance and drug toxicity. It is now used mainly for malaria prophylaxis in combination with proguanil.[6,7]

Research shows that in addition to anti-inflammatory and immunomodulatory action, HCQ can improve vascular risk by acting directly on the lipid profile and has antithrombotic properties.[8,9] It has also been proven to have an in-vitro antiviral effect on various RNA viruses.[9] Its antiviral action is exerted through the drug's accumulation and alkalinization of the endosome, lysosome, and Golgi vesicles, leading to an increase in the pH resulting in enzyme dysfunction, thus making it impossible for vesicles containing a virus to enter the cell.[9]

Owing to these properties, the year 2020 saw an emergence in the use of HCQ as an emergency-use drug to treat COVID-19, although no proper randomized controlled trial had been completed at that time to support the drugs' safety and efficacy in this COVID-19 population.[9] Its use declined due to directives from the FDA indicating no evidence that HCQ is effective against COVID-19.[9]

Adding a hydroxide derivative to CQ allowed HCQ to have fewer adverse events.[10] However, adverse reactions are seen, the most common being gastrointestinal

Clinical Points

- Hydroxychloroquine (HCQ) is used in the treatment of chronic diseases like rheumatoid arthritis and systemic lupus erythematosus.
- HCQ is associated with neuropsychiatric adverse effects like depression, mania and hypomania, anxiety disorders, suicidal ideation, psychosis, sleep disturbances, cognitive impairments such as confusion, disorientation, memory problems, and other behavioral changes like irritability and restlessness.
- Clinicians can familiarize themselves with these psychiatric side effects in patients and collaborate with psychiatrists for further evaluation and treatment.

disturbances, intravascular hemolysis, retinal toxicity, rash, and bone marrow suppression. Neuropsychiatric side effects are not rare with HCQ.[6] Historically, these were reported dating back to the 1970s. Neuropsychiatric adverse reactions include agitation, insomnia, confusion, mania, hallucinations, paranoia, depression, catatonia, psychosis, and suicidal ideation.[11,12] These adverse effect profiles have suggested caution when HCQ is prescribed.[13,14] Hence, our review's primary focus is to summarize the available evidence about HCQ-induced psychiatric side effects and their management to support physicians in clinical settings.

METHODS

A literature search of English-language articles was conducted in PubMed, MEDLINE, PsycINFO, and Cochrane Collaboration databases from 2000 to 2024. Keywords included "hydroxychloroquine" AND "psychiatry," "psychosis," "depression," "anxiety," "bipolar disorder," "delirium" OR "psychotic disorders," "psychiatric side effects," "psychiatric disorders." A study was included if it reported psychiatric side effects/adverse reactions due to HCQ use. Some studies reported neuropsychiatric side effects and did not provide a clear distinction between neurological and psychiatric side effects. They were also included in this study.

The authors (M.J.S., R.K.K., P.S., N.P.) assessed the studies for relevance to inclusion in the study, and the data were entered into an Excel sheet. Duplicate records and studies reporting only CQ side effects were excluded from the study. Studies not reporting HCQ psychiatric/neuropsychiatric side effects were also excluded.

The following data were extracted from the studies wherever possible: sociodemographic data, HCQ use, psychiatric/neuropsychiatric side effects/adverse reactions, frequency and severity of symptoms, and management of such effects. Study Quality Assessment Tools by NIH (National Heart, Lung, and Blood Institute)[15] was used to assess the quality of the included studies. This systematic review adhered to the PRISMA 2020 guidelines.[16]

RESULTS

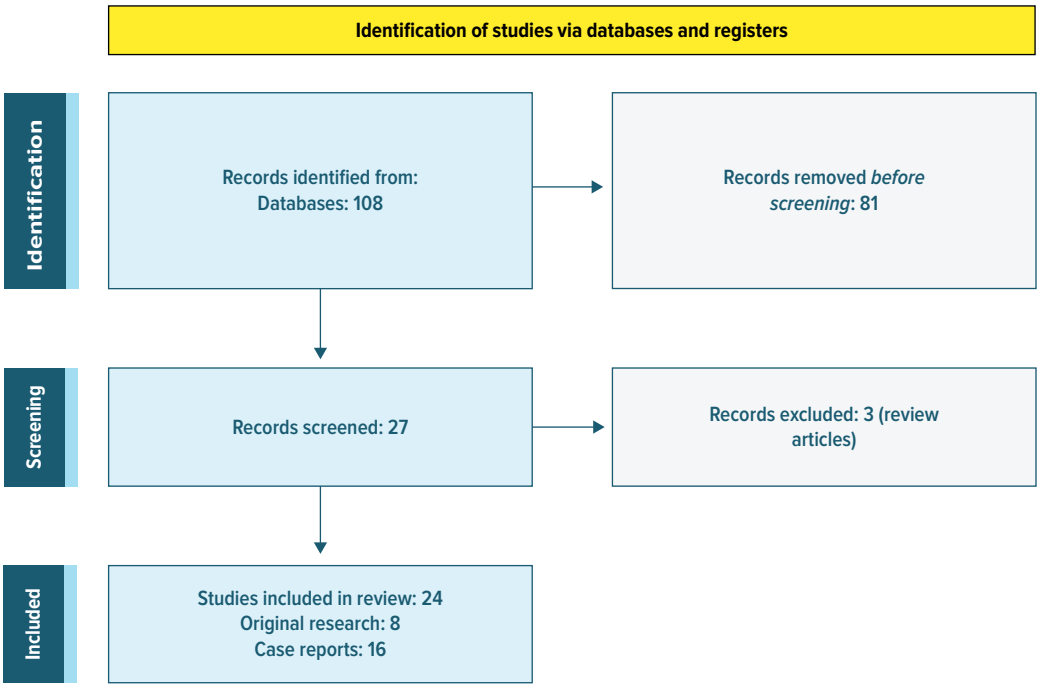
A total of 108 articles was found using the inclusion criteria. After applying exclusion criteria, 27 articles were identified. There were 16 case reports, 8 original articles, and 3 review articles. The 3 review articles were excluded, leaving a final total of 24 articles.[17–40] The PRISMA flow diagram in Figure 1 outlines this process and breaks down the reasons for the exclusion of ineligible studies. The characteristics of the case reports are included in Table 1, and the reports are summarized in Table 2.

Summary of the Original Articles

Two original articles reported significant psychiatric side effects with HCQ, and 3 articles sought to assess psychiatric adverse effects (PAEs) by analyzing existing electronic health records or adverse event reporting data (Table 3).

In a naturalistic study by Pinho de Oliveira Ribeiro et al,[34] patients taking HCQ exhibited more signs and symptoms of anxiety when compared with methotrexate and leflunomide. They also had anxiety, depression, and suicidal ideation scores above those found in the general population. Further, a bivariate analysis by Gasnier et al[35] within propensity score–matched cohorts revealed that HCQ was associated with significant anxiety symptoms, observed in 50% of the HCQ group compared to 20.1% in the control group (odds ratio [OR] = 3.8, 95% CI, 1.3–11.3, $P = .01$). HCQ was also linked to prolonged anxiety symptoms up to 4 months after acute COVID-19 infection. In contrast, PAEs were less common with treatments such as anti-interleukin-6, which were more associated with depressive symptoms, and corticosteroids, which showed no significant link to psychiatric symptoms. Garcia et al[36] conducted a pharmacovigilance analysis involving 1,754 COVID-19 patients treated with HCQ, and 56 PAEs were reported. Half of these were classified as serious, including 4 suicides, 3 instances of intentional self-injury, and 12 cases of psychotic disorders characterized by hallucinations, agitation, or aggression. The risk of developing psychiatric disorders with HCQ was significantly higher compared to other COVID-19 treatments like remdesivir, tocilizumab, and lopinavir/ritonavir, with a reporting OR of 6.27 (95% CI, 2.74–14.35). These adverse effects were more prevalent in men, with a mean age of 54.9 years, and typically appeared within a median of 5 days of starting HCQ treatment. The majority of serious psychiatric cases

Figure 1.
Study Selection Flow Diagram Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses



occurred at a dosage of 400 mg/day. In the observational cohort study by Lane et al,[37] no consistent psychiatric side effect risk (such as depression, suicidal ideation or suicide, acute psychosis) was observed in the short term in patients on HCQ compared to sulfasalazine when electronic health records and administrative claims data were analyzed. Also, no consistent long-term risk for suicidal ideation/depression was observed with HCQ compared to sulfasalazine. Nagaraja et al[17] conducted a retrospective, cross-sectional study by screening 166 patients taking HCQ prophylaxis for adverse reactions. Psychiatric manifestations were reported in 4.8% of the patients, including hypersomnolence in 4 (2.4%) patients, nervousness in 2 (1.2%), and nightmares and anxiety in 1 (0.6%).

The Effect of HCQ on Cognition

In a pilot feasibility study by Aisen et al,[38] comparing HCQ use alone and HCQ plus colchicine use in patients with Alzheimer disease, no significant changes in behavioral measures, including the Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADAS-noncog, Brief Psychiatric Rating Scale, and Hamilton Depression Rating Scale, were seen on a HCQ dosage of 400 mg for 14 weeks.

Suntoko et al[39] conducted a double-blind, randomized controlled trial to assess the influence of HCQ on improving cognitive function and inflammation in patients' SLE with cognitive dysfunction while comparing HCQ with standard therapy. They found that HCQ showed no significant effect on cognition at a dose of 200 mg for 8 weeks.

Are There Any Beneficial Effects of HCQ in Schizophrenia?

In a study by Desta et al,[40] the authors conducted a controlled trial to assess the beneficial effects of HCQ in schizophrenia (due to its ability to inhibit the activity of phospholipase A2). This study failed to show any effect on treatment status (based on the Positive and Negative Syndrome Scale [PANSS]) during the 8-week double-blind period while comparing HCQ plus standard antipsychotic therapy and placebo plus standard antipsychotic therapy. Open-label treatment for the next 12 weeks also produced no further improvement in PANSS.

Although an article by Sato et al[41] showed significantly higher reports of delirium, loss of consciousness, amnesia, hallucinations, and depression in the CQ plus HCQ group, it was not included in the study, as it did not differentiate between CQ and HCQ psychiatric adverse drug reactions.

DISCUSSION

This systematic review, to our knowledge, is the first to compare pre- and post–COVID-19 literature about the PAEs of HCQ. We sought to review the studies' pre– and

Table 1.
Characteristics of the Identified Case Reports

Characteristics	Results
Age	17–82 y Mean: 52.62 y Median: 50.5 y
Sex	Female: 13 Male: 3
HCQ indication	Rheumatoid arthritis: 5 Lupus: 4 COVID-19: 3 Other: 4
HCQ dose	100–400 mg Mean: 284.21 mg 200 mg: in 9 instances 400 mg: in 9 instances
Psychiatric adverse drug reaction onset	2 days–8 y Mean: 10 months Median: 10 days
	2 days–4 months (excluding outliers) Mean: 25.11 days Median: 7 days
Symptomatology	Psychotic symptoms: 15 Hallucinations: 13 Agitation/aggression: 6 Suicidal ideation/attempt: 3
Management	Stop HCQ + psychotropic: 9 Stop HCQ alone: 4 Other: 3
Psychotropics used	Risperidone (1–8 mg): 5 Olanzapine (5–20 mg): 5 Haloperidol (1–5 mg): 3 Benzodiazepines: 3
Symptom remission	<1 day–60 days Mean: 12.66 days Median: 7 days
Past psychiatric history	None reported: 14 Borderline personality: 1 Cannabis abuse: 1

Abbreviation: HCQ=hydroxychloroquine.

post–COVID-19 (the year 2020) and summarized our findings. HCQ is associated with psychiatric adverse reactions, primarily insomnia, anxiety, depression, and psychotic disorders, with a median onset time of 5 days from the initiation of medication.[3] In the pre–COVID-19 period, HCQ was mainly used to treat conditions such as rheumatoid arthritis (RA) and SLE that require long-term medication use. For a brief duration, HCQ was used for COVID-19 treatment before further evidence emerged that it is ineffective against severe acute respiratory syndrome coronavirus 2.

Among the various adverse effects reported from HCQ, suicide was cited as the leading cause of death before the year 2020. Given the neurotropic impact of CQ/HCQ, all studies recommend informing patients and their relatives about this possible increase in suicide risk.[29] In our review, we found that after 2020, anxiety was the most commonly reported PAE of HCQ. Before 2020, there was a higher propensity for psychiatric adverse reactions like insomnia, anxiety, and depression in women. In the case reports, women (n = 13) more than men (n = 3) were reported to have PAEs. This may be because of the use of HCQ in women for SLE and RA.[36] After 2020, given the brief increase in the use of HCQ in males for COVID-19 management/prophylaxis, an increasing number of adverse effects is also being reported in men.[36] Of the 3 case reporting adverse drug reactions while on HCQ for COVID-19, 2 of the patients were male, and 1 was female. Self-harm and suicide risk stayed comparable pre– and post–COVID-19. This could suggest that PAEs associated with HCQ may be consistent in both genders.

We further looked into risk factors for developing psychiatric side effects. One such factor could be a higher dosage of HCQ, and the use of concomitant cytochrome P3A4 (CYP3A4) inhibitors may increase the risk of psychiatric side effects.[18,36,42] Another possible risk factor is old age. The mean age of patients in the case reports is 52.62 years. The mean age of patients on HCQ in most articles included in the study ranges from 33 to 68 years, reflecting the probability of HCQ use in a slightly older population owing to the later onset of rheumatoid arthritis and lupus erythematosus. This can also be explained by possibly diminished neuronal reserve and the presence of mixed neurodegenerative and vascular brain injuries in the elderly, leading to PAEs.[29]

Mechanism of Action of HCQ and How Psychiatric Side Effects May Develop

Multiple mechanisms have been postulated to explain the occurrence of PAEs from HCQ. Further research is needed to understand the definitive causation. Inhibition of acetylcholinesterase, inhibition of prostaglandin synthesis, prostaglandin E antagonism, and imbalance in the dopaminergic pathway have been reported.[14,21] HCQ also causes neurotoxicity,[19,43–45] *N*-methyl-D-aspartate excitotoxicity, and γ-aminobutyric acid inhibition.[19,45,46] The enhanced dopaminergic activity causes symptoms of mania, psychosis,[21,47] and bipolar-like symptoms.[48] HCQ affects not only the dopaminergic pathway but also the cholinergic pathway by inhibiting acetylcholinesterase[12,44] and muscarinic receptors.[19] The net result is increased serotonin levels in the synapse, resulting in mania and psychosis.[49] Its accumulation in the brain can disrupt neurotransmitter signaling circuits (neurochemical interference with calcium signaling in neural cells as well as disruption of dopamine and acetylcholine homeostasis) involved in the pathogenesis of suicide. Its metabolic and cardiovascular impacts can result in abnormal cortisol

Table 2.

Summary of Case Reports

HCQ indication	Study	Age/sex	Maximum HCQ dose	Neuropsychiatric adverse drug reaction	Symptom remission	Psychiatric history
Rheumatoid arthritis	Kwak et al,[23] 2015	74/ Female	200 mg	Auditory hallucinations as well as persecutory, partition, and bizarre delusions	HCQ stopped + risperidone 1.5 mg	HCQ stopped + risperidone 1.5 mg
	Altintas,[24] 2015	73/ Female	400 mg	Agitation, disorganized speech, and visual and auditory hallucinations	HCQ stopped + olanzapine 5 mg	No
	Manzo et al,[25] 2017	80/ Female	200 mg	Psychomotor agitation and physical and verbal violence	HCQ stopped + promethazine 25–30 mg	No
	Ali and Jones,[26] 2018	82/ Female	400 mg	Physically aggressive and verbally abusive	HCQ stopped	No
	Gurbuz-Ozgur et al,[32] 2014	51/ Female	200 mg	Insomnia, auditory hallucinations, perspective and reference delusions, impairment in judgment	HCQ stopped	Not reported
Systemic lupus erythematosus	Hsu et al,[19] 2011	49/ Female	100 mg	Temporospatial disorientation followed by depersonalization and cenesthetic hallucinations	Risperidone	No
	Gonzalez-Nieto and Costa-Juan,[22] 2015	36/ Female	200 mg	Generalized anxiety, suicidal ideation, and the appearance of auditory and kinesthetic hallucinations	HCQ stopped + risperidone	BPD, depression, and anxiety
Dermatomyositis	Leto and Sostre,[33] 2022	55/ Female	200 mg	Altered mental status, visual hallucinations, and acute behavioral changes including inability to maintain activities of daily life, aggression	HCQ stopped Risperidone 0.5 mg by mouth twice/d	Not reported
Discoid lupus erythematosus with Raynaud's phenomenon	Cravero et al,[31] 2021	17/ Female	400 mg	Asthenia, headaches, nightmares, sadness, suicide attempt, persecutory delusions, inappropriate laughter, thought blocking, and anxiety	HCQ stopped Risperidone 8 mg/d, alprazolam 0.25 mg/d	Cannabis abuse (smoke inhalation)
Discoid lupus erythematosus	Ganjei and Bahmani,[28] 2021	37/ Female	200 mg	Auditory and visual hallucinations, nightmares	HCQ stopped	No
Q fever	Das et al,[21] 2014	43/Male	400 mg	Visual, tactile, and auditory hallucinations, ideas of reference	HCQ stopped Haloperidol and olanzapine	No
Undifferentiated connective tissue disease	Bozkirli et al,[20] 2013	23/ Female	400 mg	Visual hallucinations, persecutory ideations	HCQ stopped	No
Erosive plantar lichen planus	Ferraro et al,[18] 2004	75/ Female	400 mg	Temporospatial disorientation followed by depersonalization and cenesthetic hallucinations	HCQ stopped	No
COVID-19	Boulos et al,[27] 2020	50/ Male	400 mg	Psychomotor agitation, auditory hallucinations	Haloperidol 2.5 mg by mouth twice/d	No
	Costanza et al,[29] 2021	54/Male	400 mg	Depressive symptoms with melancholic features and severe suicidal ideation	HCQ stopped Sertraline and olanzapine	No
	Yesilkaya et al,[30] 2021	43/ Female	400 mg	Psychomotor agitation, physically aggressive behavior at home, auditory hallucinations, and insomnia	Olanzapine	No

Abbreviations: BPD = borderline personality disorder, HCQ = hydroxychloroquine.

release and arrhythmia, both of which have been linked to increased suicide risk.[29] Additionally, there is a downregulation of glycoprotein-P in the blood-brain barrier. Glycoprotein-P is responsible for clearing various substances from neurons and clearing antidepressants along the blood-brain barrier.[49] Therefore, a patient on antidepressants and having mental health disorders could have a variation in their mental health status when on HCQ. HCQ decreases seizure threshold when used along with psychotropics like clozapine and chlorpromazine. It increases the electroencephalogram frequencies acting as a

Table 3.

Summary of the Original Articles

Study	Objective	Primary diagnosis	Population groups	Sample size[a]	Age (mean), y	HCQ dose	HCQ use/study duration	Information collection methods	Results	Remarks/notes
Aisen et al,[38] 2001	Assess HCQ potential to cause adverse physical, cognitive, and behavioral effects in subjects with AD	AD	HCQ only HCQ and colchicine	11 (4/7) 9 (5/4)	68 ± 9 68 ± 8	400	14 wk	Trained psychometrician interview	No significant (within subjects) changes in behavioral measures, including ADAS-noncog, BPRS, and HDRS	Pilot study with low sample size. Subjects were relatively young (for an AD patient), with a mean age less than 70 y
Desta et al,[40] 2002	Assess beneficial effects of HCQ in schizophrenia (due to its ability to inhibit the activity of phospholipase A2)	Schizophrenia	HCQ plus psychotropic drug Placebo plus psychotropic drug	28 (24/4) 33 (27/6)	28.5 ± 7 31.2 ± 7.9	200	Double-blind for 8 wk + open trial for 12 wk	Physician rated	Failed to show a main effect of treatment status (based on PANSS) Open-label treatment produced no further improvement (in PANSS)	Patients enrolled in this study had prior treatment with antipsychotic drugs before taking HCQ A large improvement in symptoms by antipsychotic treatment prior to entry may have prevented the observation of a smaller effect produced by HCQ
Pinho de Oliveira Ribeiro,[34] 2013	To investigate the prevalence of anxiety, depression, and suicidal ideation in patients with RA taking different drugs to control the disease	RA	HCQ Methotrexate Leflunomide Biological drugs	31 (1/30) 21 (5/16) 42 11	61.74 52 57.21 66.55	NR NR NR NR	NR	Physician-rated scales: HADS, Beck Suicide Inventory	Patients using biological drugs and HCQ exhibited more signs and symptoms of anxiety The HCQ group showed intermediate averages on the HADS-A, indicating probable anxiety, with very high scores for suicidal ideation on the Beck Suicide Inventory	All groups had scores (anxiety, depression, and suicidal ideation) above those found in the general population
Garcia et al,[36] 2020	Assess the psychiatric adverse effects of HCQ in COVID-19 patients	COVID-19	Adverse effects with HCQ Adverse effects with other drugs	56 (27/25/5) 17 (7/10)	54.9 61.9	200–800 (400 in 70%)	1 d–27 d (median: 10 d)	VigiBase study from January 2020 to June 16, 2020	28 serious adverse events, of which 4 suicides, 12 hallucination and agitation cases, 7 cases of insomnia or anxiety, 2 confusion cases, and 3 intentional self-injury cases have been attributed to HCQ	Use of HCQ was associated with increased risk of psychiatric disorders in treating COVID-19 compared to other drugs (remdesivir, tocilizumab, and lopinavir/ritonavir)
Lane et al,[37] 2021	Assess risk of suicide, depression, and psychosis associated with HCQ for RA	RA	HCQ Sulfasalazine	918,144 290,383	18+ 18+	NR	30-d follow-up plus long-term follow-up	Electronic health records and administrative claims data	No consistent short-term/long-term risk for suicidal ideation/depression was observed with HCQ compared to sulfasalazine	HCQ is compared to sulfasalazine in treatment of RA, hence standalone psychiatric manifestations of HCQ cannot be commented on
Nagaraja et al,[17] 2020	Assess adverse event profile of HCQ prophylaxis for COVID-19 in health care workers	COVID-19	Prophylactic HCQ	166 (122/44)	36.3 ± 11.8	NR	NR	Web-based semistructured questionnaire	Psychiatric adverse events included hypersomnolence: 4 (2.4%), nervousness: 2 (1.2%), nightmares: 1 (0.6%), and anxiety: 1 (0.6%)	Beyond the first week of therapy, participants with side effects were not included to limit recall bias

(continued)

Table 3 (continued).

Study	Objective	Primary diagnosis	Population groups	Sample size[a]	Age (mean), y	HCQ dose	HCQ use/study duration	Information collection methods	Results	Remarks/notes
Gasnier et al,[35] 2022	Assess psychiatric symptoms of COVID-19 patients treated with HCQ, IL-6 antagonists, and steroids	COVID-19	Received treatment with HCQ No treatment	18 (4/14) 132 (75/57)	57.55 ± 11.5 57.0 ± 13.9	Mean dose 427.3 mg/d	4 mo	EMR, self-assessment questionnaires, Insomnia Severity Index, HAD-A, BDI-13, PTSD Checklist for *DSM-5*, MINI by trained physician	In patients taking HCQ 4 months after COVID-19, 4 developed insomnia, 9 developed anxiety, and 4 developed depression; 5 patients were diagnosed with MDD and 2 with anxiety disorders	HCQ can lead to long-lasting psychiatric symptoms, especially anxiety
Suntoko et al,[39] 2023	Assess the influence of HCQ on improving cognitive function and inflammation in SLE compared to standard therapy	SLE with cognitive dysfunction	HCQ plus standard therapy Standard therapy	26 29	33.00 ± 10.53 34.55 ± 8.15	200	Double-blind study for 8 wk	Montreal Cognitive Assessment	HCQ showed no significant effect on cognition	Low sample size may be the reason for the noninfluence of HCQ on cognition

[a]Male, female, and other.
Abbreviations: AD = Alzheimer disease, ADAS-noncog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, EMR = electronic medical record, HADS = Hospital Anxiety and Depression Scale, HCQ = hydroxychloroquine, HDRS = Hamilton Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview, NR = not reported, PANSS = Positive and Negative Syndrome Scale, PTSD = posttraumatic stress disorder, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

cerebrocortical stimulant[50] but decreases voltage, which may trigger seizures.[51]

Role of Pharmacokinetics and Drug Interactions in PAEs of HCQ

HCQ and CQ have a long half-life in the blood, approximately a month.[12,40,41,52] Although considered relatively safer drugs, they have a narrow therapeutic index.[13,53,54] CQ/HCQ exhibits neurotropism, as its level in the CNS was shown to be 10–30 times higher than its serum concentration after dosing.[13,55] It is completely absorbed in the system within 2–4 hours after oral administration,[54] which can lead to various psychiatric adverse reactions like acute psychosis, mania, depression, anxiety, and suicidal ideations.[53]

Variations in absorption, degradation, and consequent differences in the drug's steady-state concentration may lead to variability in the time window between drug intake and PAE manifestation.[24,25,54,56] Concomitant corticosteroid use and a family history of psychiatric disorder can increase the risk of developing PAEs.

When CQ or its analogs are used with psychotropics with CYP3A4 inhibitory potential, side effects will ensue due to raised levels of CQ. CYP3A4 inducers could decrease levels of CQ or HCQ. The combined cardiac side effects of CQ analogs must be kept in mind when prescribed in conjunction with psychiatric medications that prolong QTc interval with the resulting cumulative cardiotoxicity.[52,57] The risk of PAEs was particularly signalized among patients in cotreatment with metformin.[29,58]

There are many areas in psychiatric treatment where caution must be exerted.[20] In particular, when HCQ is prescribed for chronic medical conditions, a psychiatric review of symptoms and monitoring for any appearance of PAEs is recommended. Psychiatry consultants must be aware of these side effects and guide the management. When side effects occur, stopping HCQ and the addition of psychotropics such as olanzapine, risperidone, and haloperidol were reported as successful interventions for the resolution of symptoms.[21,59] Psychotropic drugs must be used, making sure to avoid SLE-inducing drugs, such as chlorpromazine, carbamazepine, and lithium carbonate.[59]

Limitations of the Study

The first limitations of our study are publication bias, selection bias, attrition bias, inadequate blinding, and selective outcome reporting. Duplicate references, transcription errors, and accidental inclusions or exclusions can skew or invalidate the results of our review, which we have minimized to the best of our ability.

Second, it is not uncommon for patients to develop mental health disorders such as depression and anxiety as a long-term sequela of the chronic disease. Recent studies indicate a higher prevalence

(13%–47%) of depression and anxiety disorders in patients with RA compared to the general population, with symptoms sometimes leading to panic attacks, low self-esteem, and suicidal trends.[19,45,46] The chronic nature of RA and SLE can worsen the prognosis of comorbid psychiatric disorders.[19,47] Conditions such as rheumatoid arthritis require long-term medications, including drugs like HCQ, which can confound HCQ-induced PAEs.

The third limitation is that symptoms of a neuropsychiatric nature in patients with COVID-19 may not always be drug induced and instead caused by the huge cytokine storm due to the disease process and neuroinflammatory mechanisms.[60] Some evidence points towards external stressors as the reason for the rise of PAEs in patients who took HCQ for COVID-19.[25] This would skew our data for the causation-effect relationship of HCQ-induced PAEs in COVID-19 patients.

Strengths of the Study

First, we included literature up to year 2024, which combined the reporting of side effects during COVID-19 treatment. Second, we sought to explore various presentations of the PAEs and how they were managed.

CONCLUSION

HCQ is a commonly prescribed medication for chronic medical conditions like RA and SLE. HCQ has been associated with a few psychiatric side effects such as depression, mania and hypomania, anxiety disorders, suicidal ideation, psychosis, insomnia, cognitive impairments like confusion, disorientation, memory problems, and other behavioral changes like irritability and restlessness. The onset of these psychiatric side effects can vary in duration. In our review, we found a propensity in the usage of second-generation antipsychotics, particularly olanzapine and risperidone, for the treatment of these PAEs. Haloperidol was also helpful in some cases. Further investigative studies and clinical trials are needed to understand the mechanisms behind the causation of these side effects from HCQ.

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