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Review Article

Psychiatric Aspects of Chloroquine and Hydroxychloroquine Treatment in the Wake of Coronavirus Disease-2019: Psychopharmacological Interactions and Neuropsychiatric Sequelae

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Background: *Chloroquine and hydroxychloroquine are among several experimental treatments being investigated in the urgent response to the coronavirus disease-2019. With increased use of these medications, physicians need to become knowledgeable of these drugs' neuropsychiatric side effects and interactions with psychiatric medications.* **Objective:** *Clarify evidence base regarding the psychiatric side effects and psychiatric drug interactions of chloroquine and hydroxychloroquine.* **Methods:** *A literature review was performed in PubMed from 1950 to 2020 regarding psychiatric topics and targeted pharmacological properties of chloroquine and hydroxychloroquine.* **Results:** *First, chloroquine and hydroxychloroquine may mildly inhibit CYP2D6 metabolism of psychiatric medications, and psychiatric medications that interfere with CYP2D6 or CYP3A4 activity could alter chloroquine and hydroxychloroquine levels. Second, they may prolong the QT interval, warranting caution with concomitant prescription of other QT prolonging agents. Finally, neuropsychiatric side effects are very uncommon but possible and include a potentially prolonged phenomenon of "psychosis after chloroquine." Hydroxychloroquine has less information available about its neuropsychiatric side effects than chloroquine, with psychosis literature limited to several case reports. Weak evidence suggests a possible association of hydroxychloroquine exposure and increased suicidal ideation. It is not clear whether patients with psychiatric illness are more vulnerable to neuropsychiatric sequela of these medications; however, overdose of these medications by suicidal patients has high risk of mortality.* **Conclusion:** *The risk of neuropsychiatric side effects of chloroquine and hydroxychloroquine when used for coronavirus disease-2019 treatment is not known. Best practice may include suicide risk assessment for patients treated with hydroxychloroquine. However, delirium is expected to be a more likely etiology of neuropsychiatric symptoms in critically ill patients treated for coronavirus disease-2019, and adjustment disorder is a much more likely etiology of anxiety and depression symptoms than the side effects of chloroquine or hydroxychloroquine.*

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Key words: chloroquine, hydroxychloroquine, psychiatry, neuropsychiatry, COVID-19.

INTRODUCTION

Chloroquine was developed subsequent to the bark extract quinine for the treatment and prophylaxis of malaria.[1] Owing to potential toxicity and drug resistance, chloroquine and quinine are no longer in frequent use.[2] Both chloroquine and hydroxychloroquine are

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currently under investigation as possible treatments for patients infected with severe acute respiratory syndrome coronavirus 2 (which causes the disease coronavirus disease-2019 [COVID-19]). Several mechanisms have been suggested to explain how chloroquine and hydroxychloroquine may be therapeutic for COVID-19,[3,4] including inhibition of viral binding to the host cell ACE2 receptor (is the mechanism for viral entry into host cells), inhibition of viral replication enzymes via raising host cell organelle pH, and de-escalation monocyte cytokine production (decreasing immune-mediated host tissue damage). These mechanisms could serve to inhibit virus entry into neurons and glia, slow replication of the virus in the brain and other tissues, and de-escalate the neuroinflammatory response (and delirium risk).

Chloroquine and hydroxychloroquine have been shown to inhibit severe acute respiratory syndrome coronavirus 2 *in vitro*.[5,6] A Chinese commentary reported early favorable results in placebo-controlled trials of chloroquine treatment of COVID-19,[7] and based on this early data, the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province has published chloroquine dosing recommendations for COVID-19.[8] Others have published recommendations to consider hydroxychloroquine instead of chloroquine for COVID-19 treatment, citing a superior side effect profile.[9] Higher mortality was shown with COVID-19 treatment using higher dose chloroquine (600 mg twice daily) relative to a lower dose (450 mg twice daily) in a phase II double-blinded, randomized clinical trial.[10] One large registry found increased mortality with chloroquine treatment, as well as increased risk of ventricular arrhythmia.[11] Likely owing to the appeal of hydroxychloroquine's superior side effect profile relative to chloroquine, more research is currently published on hydroxychloroquine treatment of COVID-19. One placebo-controlled randomized trial of 62 patients showed faster COVID-19 recovery time with hydroxychloroquine than placebo,[12] and a large retrospective study suggested hydroxychloroquine benefits and minimal adverse effects.[13] In contrast, many observational studies have not detected a mortality benefit with hydroxychloroquine treatment of COVID-19,[14–17] and some studies even have suggested net adverse outcomes with hydroxychloroquine treatment for COVID-19 (cardiac, gastrointestinal).[11,14,16,18]

In summary, chloroquine and hydroxychloroquine are not clearly evidenced to be beneficial in treatment of COVID-19 at this time, but are under further investigation and are being used (more hydroxychloroquine in the United States) in the setting of highly limited treatment options. Psychiatrists and other physicians may encounter patients on chloroquine and hydroxychloroquine for COVID-19 treatment, and this review aims to summarize the current psychiatric research on these medications to enable physicians to clarify what drug-drug interactions and possible neuropsychiatric side effects may need to be considered in clinical care.

Chloroquine and hydroxychloroquine have been in clinical use for more than 50 years,[19] and both historic and current data relevant to psychiatry are presented. First, pertinent pharmacokinetic considerations and drug-drug interactions are discussed. Second, potential for QT prolongation is reviewed. We then provide an overview of central nervous system (CNS) side effects of chloroquine and hydroxychloroquine, followed by a comprehensive description of the current literature on neuropsychiatric side effects of chloroquine and hydroxychloroquine. Finally, more common alternate etiologies for psychiatric presentations in hospitalized patients with COVID-19 are briefly discussed.

SEARCH STRATEGY

References for this review were identified through searches performed in PubMed for articles published from January 1950 to March 2020, combining the terms "chloroquine" and "hydroxychloroquine" with terms "psychiatry," "neurology," "neuropsychiatry," "depression," "anxiety," "psychosis," "delirium," "encephalopathy," "memory," "suicide," "CYP450," and "QTc." Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles were included with novel or recent content.

PSYCHIATRICALLY RELEVANT PHARMACOLOGY

Pharmacokinetics and Drug Interactions

Both chloroquine and hydroxychloroquine have a large volume of distribution with variable but prolonged elimination half-lives, ranging from 40 to 60 days.[19] Chloroquine is known to be a mild 2D6 inhibitor[20] and a substrate for CYP2C8 and CYP3A4, with minor CYP2D6 metabolism.[21] Hydroxychloroquine is also a mild inhibitor of CYP2D6, and is metabolized by similar

TABLE 1. Psychiatric Medications that may Alter Chloroquine or Hydroxychloroquine Metabolism by Altering CYP2D6 or CYP3A4 Metabolism

Interactions*,†	Alter CYP2D6 metabolism	Alter CYP3A4 metabolism
Strong inhibitors	Bupropion, fluoxetine, paroxetine	None
Moderate inhibitors	Sertraline, duloxetine	None
Weak inhibitors	Citalopram, escitalopram	Atomoxetine
Inhibitors of unclear strength	Clomipramine, doxepin, moclobemide, haloperidol, perphenazine, hydroxyzine, diphenhydramine, methadone	Fluvoxamine
Inducers	None	Barbiturates, carbamazepine, oxcarbamazepine, modafinil

*Interactions listed are based on the Drug Interactions Flockhart Table.[23]

†No psychiatric medications are known to be significant CYP2C8 inhibitors or inducers.

TABLE 2. Psychiatric Medication–Vulnerable Mild CYP2D6 Metabolism Inhibition by Chloroquine or Hydroxychloroquine

Drug class	Psychiatric medications metabolized by CYP2D6*
SSRIs	Citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine
SNRIs	Venlafaxine
TCAs	Amitriptyline, nortriptyline, clomipramine, imipramine, desipramine, doxepin
Antipsychotics	Haloperidol, risperidone, aripiprazole, brexpiprazole, cariprazine, pimavanserin, thioridazine
Other	Amphetamine, atomoxetine, donepezil, valbenazine, propranolol, dextromethorphan

SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressants.

*CYP2D6 substrates listed are based on the Drug Interactions Flockhart Table.[23]

CYP450s to chloroquine (CYP2D6, 2C8, 3A4, and 3A5).[22] Potential CYP450 interactions among psychiatric medications and chloroquine or hydroxychloroquine are listed in Table 1 and Table 2. In addition, both chloroquine and hydroxychloroquine are partially renally excreted and require dose adjustment when in a patient is in renal insufficiency to reduce risk of toxicity.[24] Both chloroquine and hydroxychloroquine demonstrate dose-dependent inhibition of platelet aggregation.[25,26] One study showed possible synergism for cardiovascular thromboprophylaxis with five or more years of concomitant administration of aspirin and hydroxychloroquine,[25] but we were unable to find any studies evaluating the thrombotic impact of coadministering chloroquine or hydroxychloroquine concomitantly with psychiatric medications known to inhibit platelet aggregation, such as selective serotonin reuptake inhibitors.[27]

QT Interval Prolongation

Both chloroquine and hydroxychloroquine have been suspected to prolong the QT interval; however, the clinical significance of this is unclear. Although some studies demonstrate QT prolongation, others do not.[28] A 2018 systematic review of published prospective trials with chloroquine did not demonstrate increased risk of sudden deaths attributed to cardiac arrhythmias.[29] Nevertheless, several case reports describe episodes of Torsades de Pointes (TdP) for patients on chloroquine[30] and hydroxychloroquine.[31,32] In the setting of increased cardiac vulnerability and frequent exposure to QTc-prolonging agents (e.g., azithromycin) during hospitalization for COVID-19, the U.S. Food and Drug Administration (FDA) released a drug safety communication warning that addition of hydroxychloroquine or chloroquine may increase risk of negative cardiac outcomes.[33] It is reasonable for psychiatrists to anticipate that the risk of TdP may be increased in combination with medications known to prolong the QT interval, such as antipsychotics, TCAs, or hydroxyzine (refer to Funk 2020 for a more comprehensive review of QT interval prolongation with psychiatric medications).[34] Increased risk of TdP in overdose of chloroquine or hydroxychloroquine by suicidal patients is certainly another relevant consideration for psychiatrists.

CNS Side Effects

The most common CNS side effects of chloroquine are headache (6.4%), dizziness (5.3%), and insomnia (4.5%).[35] Dose-dependent retinopathy can occur with chloroquine (less frequent with hydroxychloroquine),

and this requires monitoring with careful attention to the need for dose adjustment.[19] In general, the side effects with hydroxychloroquine are similar to those with chloroquine, but are less common.[19] Infrequent case reports have also reported dystonia and generalized tonic-clonic seizures after chloroquine administration.[35–38]

Early symptoms of CNS toxicity include nausea and vomiting, dizziness, and headache, followed by delirium and seizures.[36] Chloroquine has a narrow therapeutic window with rapid onset of toxicity symptoms[36] and a 10–35% risk of mortality in overdose,[39,40] another factor for psychiatrists to consider in patients with risk of overdose. CNS toxicity (and neuropsychiatric effects) may occur at therapeutic doses.[36,37,41] Hydroxychloroquine overdose has less data but can also be fatal.[42]

Several mechanisms of chloroquine have been proposed as contributors to chloroquine neuropsychiatric side effects: inhibition of neuronal calcium currents,[43] dopamine excess,[37,44] prostaglandin E antagonism,[45] spermidine excess,[46] and acetylcholine dysfunction.[47] Furthermore, CNS levels of chloroquine are elevated 10–30 times over serum levels,[48] possibly influenced by interference with P-glycoprotein function in the blood-brain barrier.[49] Hydroxychloroquine is proposed to have many similar properties to chloroquine, and often hydroxychloroquine mechanisms of action are assumed based on chloroquine studies.[19,50]

Neuropsychiatric events such as depression, mania, psychosis, and catatonia are present in less than 1–2% of patients on chloroquine.[35,51,52] These events also seem to present less with hydroxychloroquine exposure than chloroquine exposure. Research regarding these phenomena is largely composed of case series and case reports and is described in the sections that follow.

NEUROPSYCHIATRIC SIDE EFFECTS

Psychosis

Although overall incidence is unknown, cases of "psychosis after chloroquine" have been described since 1958.[53] A retrospective study by Biswas et al.[41] describes 51 cases diagnosed as psychosis after chloroquine over the course of 10 years, extracted from the records of 22 psychiatric units in areas of India where malaria is hyperendemic. The inclusion criteria in this study were reasonable and included diagnostic criteria for substance-induced mood disorder, hallucinations or delusions in the absence of delirium, a minimum of 1 week of psychiatric symptoms, psychosis onset within 6 weeks of chloroquine initiation (at least one 150-mg tablet exposure), and resolution within 8 weeks of discontinuing chloroquine. Chloroquine levels were not drawn, so it is unclear what proportion of cases featured toxic levels. This study demonstrated that these psychosis presentations most commonly featured combined psychotic and affective symptoms (76.2% of cases). The most prevalent affective presentation was irritability with a mixed mood episode. Consistent with case series before this study,[37,38] psychotic episodes were demonstrated to be prolonged (mean duration to resolution was 29.62 days after discontinuation of chloroquine).[41] Psychosis after chloroquine is often described to feature derealization or depersonalization,[37,41,48] and the study by Biswas et al.[41] found this was mostly present in the context of psychosis onset after significant stressors. The most common positive symptoms in the study were visual hallucinations, and most cases did not feature negative symptoms.[41] In addition, psychosis after chloroquine is typically not related to premorbid psychiatric history, and patients are reported to have preserved insight during psychosis after chloroquine.[37,41,48] A dose-response relationship between chloroquine dose and risk of psychotic symptoms has not been demonstrated.[41] Chloroquine's prolonged half-life and high CNS penetration are mechanisms proposed to explain the prolonged psychotic symptoms course after chloroquine discontinuation.[37,41]

No studies were found regarding the incidence of hydroxychloroquine-induced psychotic symptoms. Six case reports describe psychosis suspected to be associated with hydroxychloroquine in diverse circumstances and were temporally related by hydroxychloroquine prescription preceding the onset of psychosis and resolving with hydroxychloroquine discontinuation. Hydroxychloroquine was prescribed for lupus presentations in three of these cases.[54] In one report, the patient was suspected to have CNS toxicity owing to a pharmacy error resulting in 10-day exposure to an excessive hydroxychloroquine dose.[40] Another case featured a patient with borderline personality disorder who developed auditory and kinesthetic hallucinations, as well as suicidal ideation during two hydroxychloroquine exposures that were five years apart.[55] It is not clearly documented in all cases how lupus cerebritis was ruled out as a psychosis etiology, but one author

used the Naranjo probability scale to evidence a hydroxychloroquine-induced psychosis etiology.[56] The other three cases describe diverse psychotic presentations in the setting of hydroxychloroquine treatment for rheumatoid arthritis,[57] Q fever,[50] and erosive plantar lichen planus.[58] The patient with rheumatoid arthritis developed disorganized psychosis with neurovegetative features.[57] Another patient being treated for Q fever demonstrated an array of hallucinations (auditory and visual as well as formication) without disorientation or fluctuation of alertness.[50] The final case was notable for concomitant methylprednisolone exposure, as well as an atypical psychotic presentation: early nightmares followed by depersonalization and cenesthetic hallucinations (false perception of viscera movement).[58]

Mood Disorders

Mood episodes may occur without psychotic symptoms associated with chloroquine or hydroxychloroquine exposure. In a 1962 case series by Drew,[59] 43% of 21 patients treated with chloroquine for rheumatoid arthritis developed mild-to-severe depression, with one patient's depression being severe enough to warrant electroconvulsive therapy. The presence of rheumatic diseases could be a confounder for depression etiology in this small case series. Larger sample, malaria chemoprophylaxis studies do not demonstrate association of chloroquine exposure with such high incidence of depressive symptoms, although it is feasible that the higher doses of chloroquine used in treatment of rheumatological conditions could present an increased risk of incident depression than the lower doses used in malaria chemoprophylaxis. In a 1993 study evaluating a database of 40,726 patients on antimalarial chemoprophylaxis with chloroquine 300 mg weekly, depression was documented in 1.4% of the patients.[35] Of note, the chloroquine dosing in this study is less than the dosing being used for COVID-19 treatment. In a 2009 four-arm, randomized, double-blinded, placebo-controlled study of mood profiles during malaria chemoprophylaxis, the study arm with 154 patients treated with chloroquine did not demonstrate increased depression symptoms, compared with controls.[60] Of note, the chloroquine dose in this study (100 mg per day) is less than that being used for COVID-19. Furthermore, the study's placebo group only took placebo for the first 1 week of a more than 6-week trial (transitioned to drug exposure after 1 wk), decreasing the validity of the placebo comparison. Finally, a 2013 nested case-control analysis of over 7 years of data from the United Kingdom General Practice Research Database demonstrated that the 34 cases of incident depression while on chloroquine chemoprophylaxis did not reflect a significant difference in depression risk compared with controls.[53] A problematic feature of this study was that an incident case of depression would be linked to chloroquine if exposure was within 540 days before general practitioner diagnosis of depression, which seems like an inappropriately long duration at ascribe association.

Despite the apparent low frequency of chloroquine-associated depression in malaria chemoprophylaxis studies, several case reports describe patients who developed severe depressive episodes (often with suicidal ideation and psychotic features) within days of chloroquine exposure.[38,61,62] A common feature of these cases was resolution of the depressive symptoms within several days of discontinuing chloroquine. Completed suicide via overdose on chloroquine has been previously reported, and fatal overdoses are possible at just a few times the therapeutic dose (often at 2–4 gram overdose).[62] This should evoke caution in prescription of chloroquine for patients experiencing active suicidal ideations.

Several case reports describe manic episodes during chloroquine exposure,[37,38,44,63,64] although no systematic studies are published. In these reports, onset of manic presentations was approximately 1 week after initiation of chloroquine exposure, with resolution 1–2 weeks after discontinuation of chloroquine. Classic manic symptoms were present in described cases, with notable grandiosity and frequent religiously-themed delusions. Patients were treated with haloperidol and chlorpromazine, as well as electroconvulsive therapy for one patient who developed catatonia.

Mood episodes associated with hydroxychloroquine have received less research attention. In a 2013 naturalistic study of patients receiving treatment for rheumatoid arthritis (n = 115), the 31 patients on hydroxychloroquine did not demonstrate an elevated risk for depression compared with other treatment groups.[65] However, the patients on hydroxychloroquine scored significantly higher on severity of suicidal ideation in the Beck Scale for Suicidal Ideation (mean = 16.94 ± 11.09) than patients on methotrexate or leflunomide. Severity of suicidal ideation for patients taking hydroxychloroquine was still much lower than

with exposure to the biologic therapies (e.g., rituximab; mean = 25.73 ± 3.82). Given that this was a naturalistic study, clinical features that prompted the decisions for the one treatment over another could represent confounders in group comparison, and this was not clearly controlled for in the study. It is unclear whether these data can be meaningfully generalized to the context of persons taking hydroxychloroquine for COVID-19 prophylaxis or treatment. A 2018 review by Mascolo et al.[66] evaluated the reports of hydroxychloroquine psychiatric side effects entered into the EudraVigilance pharmacovigilance database of the European Medicines Agency from 2001 to 2017. A total of 70 cases of depression and 53 cases of completed suicide were reported. Causation of these outcomes by hydroxychloroquine is certainly not clear from these pharmacovigilance data; however, the data do raise questions that warrant more formal study.

Anxiety

Anxiety has not received much attention as a psychiatric side effect of chloroquine, although several case reports have described panic episodes attributed to chloroquine exposure.[37,38] In these cases, anxiety symptoms resolved within a few days of chloroquine discontinuation. In the 1966 case series by Drew,[59] some patients described increased claustrophobia and nightmares during chloroquine exposure.[46]

In the European Medicines Agency pharmacovigilance database from 2001 to 2017, 32 cases of anxiety disorders in the setting of hydroxychloroquine exposure and 59 cases of insomnia were reported.[66] Furthermore, in the previously referenced 2013 study by Pinho de Oliveira Ribeiro et al.,[65] many of the patients on hydroxychloroquine treatment for rheumatoid arthritis were found to screen positive on the anxiety subscale of the Hospital Anxiety and Depression Scale (mean = 11, SD = 2.68). The anxiety scores in this group were significantly higher than scores of patients on methotrexate or leflunomide. Similar to the affective data from this rheumatoid arthritis treatment study, these data may not generalize well to the context of persons taking hydroxychloroquine for COVID-19 prophylaxis or treatment.

Neurocognitive Disorders

Some attention has been directed to consideration of hydroxychloroquine as an intervention for neurodegenerative disorders, based on its impact on lysosomal pH and immune system activation. A 2019 retrospective study in a large sample of patients with connective tissue disorders did not demonstrate a significant change in risk of developing Alzheimer's dementia for patients exposed to chloroquine or hydroxychloroquine.[67] Furthermore, in a 2018 double-blinded, randomized controlled trial of 168 subjects with early Alzheimer's disease, the group with 18 months of treatment with hydroxychloroquine did not demonstrate significant difference compared with the placebo regarding dementia progression, cognitive performance, or behavior changes.[68]

NEUROPSYCHIATRIC SYMPTOMS MORE EXPECTED IN PATIENTS HOSPITALIZED FOR COVID-19

Although no thorough studies on neuropsychiatric symptoms of COVID-19 have been published at the time this article was written, psychiatric presentations are expected to be common in hospitalized patients with COVID-19 because of etiologies other than chloroquine- or hydroxychloroquine-induced neuropsychiatric side effects. Delirium has, anecdotally, been frequent in patients requiring intensive care. Critically ill patients frequently become delirious and may present with confusion, aggression, mood changes, hallucinations, delusional thinking, or other neuropsychiatric symptoms.[69] In addition, survival of acute respiratory distress syndrome complicated by delirium has been associated with increased incidence of posttraumatic stress symptoms.[70] In the study by Mao et al.,[71] nervous system–related clinical findings were present in 36.4% of 214 hospitalized COVID-19 cases, with the most common findings being stroke, ataxia, seizure, and "depressed level of consciousness." Prevalence of neurological symptoms was increased to 45.5% in severe COVID-19 cases. In addition, a study of 58 patients with COVID-19 and acute respiratory distress syndrome showed that 69% of patients had agitation, and 65% were confused when neuromuscular blockade was discontinued.[72] Within the discharged subgroup in this study, 33% demonstrated executive dysfunction. In addition to the physiological impact of COVID-19 and treatment exposures (i.e., sedatives, prolonged mechanical ventilation), several authors had noted that isolation introduces barriers to nonpharmacological measures to decrease the risk of delirium.[73] Although a detailed consideration the

pathophysiology and treatment of delirium in COVID-19 is beyond the scope of this article, but comprehensive articles have been published elsewhere.[73–75] Additionally, case reports have been published regarding COVID-19 infection complicated by steroid-responsive encephalitis,[76] psychosis in patients without delirium,[77] and acute hemorrhagic necrotizing encephalopathy.[78]

Increased depression, anxiety, memory deficits, insomnia, and posttraumatic stress disorder symptoms were demonstrated in survivors of severe acute respiratory syndrome coronavirus 1 and Middle East respiratory syndrome coronavirus infections, and these may be symptoms present in COVID-19 survivors as well.[79] Furthermore, in a survey one year after H1N1 influenza-associated acute respiratory distress syndrome, survivors reported high anxiety, depression, and posttraumatic stress disorder.[80] Patients hospitalized for pandemic-related infections, who do not experience delirium, may also experience adjustment disorder with depressive and/or anxious symptoms, as well as posttraumatic stress disorder.[81] Survivors of hospitalization for pandemic-related infections may also express pessimistic views, anger due to perception of rejection by society, and survivor grief.[82] Although no COVID-19 pandemic suicidology studies have been published at the time of this writing, some authors predict increased suicidality, based on previously demonstrated correlations with increased unemployment[83] and based on increased suicide rates during the 2003 severe acute respiratory syndrome coronavirus 1 epidemic.[84] Given the high expected incidence of psychiatric presentations during COVID-19 hospitalization, the infrequent neuropsychiatric side effects of chloroquine and hydroxychloroquine may be very difficult to clinically isolate in this population, though may be more clear to isolate in the setting of prophylactic use.

CONCLUSIONS

Anticipation of potential neuropsychiatric sequela from chloroquine and hydroxychloroquine treatment of COVID-19 requires extrapolation of chloroquine and hydroxychloroquine research in treatment of rheumatological disease and chemoprophylaxis for malaria. Neuropsychiatric side effects are uncommon in patients on chloroquine and hydroxychloroquine, although they are better described with chloroquine exposure than hydroxychloroquine exposure. Psychiatric symptom presentation during hospitalization for COVID-19 infection is much more likely to be due to delirium and adjustment disorder than neuropsychiatric side effects of chloroquine and hydroxychloroquine. The most studied neuropsychiatric phenomenon with these medications is "psychosis after chloroquine," which may be prolonged in its resolution. Conversely, psychosis induced by hydroxychloroquine has been described only in a few case reports and should be expected to be quite rare. Weak evidence suggests potential for increased anxiety symptoms or suicidal ideation with hydroxychloroquine exposure, although this evidence is based on a very limited research with unclear generalization. Given that pandemic stressors and neuropsychiatric sequelae of COVID-19 could possibly synergize with this possible increased suicide risk attributable to hydroxychloroquine, best practice may include screening for suicidal ideation and performance of a suicide risk assessment for patients on hydroxychloroquine for COVID-19 prophylaxis or treatment. Appropriate clinical practice can be better clarified by future research studying the association of hydroxychloroquine with suicidal ideation and suicide attempts, particularly in the setting of COVID-19 prophylaxis or treatment. Further psychiatric considerations include chloroquine and hydroxychloroquine's mild CYP2D6 inhibition, the potential for psychiatric medications to impact chloroquine and hydroxychloroquine levels and toxicity, and the potential increased risk of TdP when chloroquine or hydroxychloroquine is combined with psychiatric medications that prolong the QT interval. The neuropsychiatric effects of chloroquine and hydroxychloroquine when used for treatment of COVID-19 have not been previously studied. Future research regarding the incidence and phenomenon of neuropsychiatric side effects in this clinical context may be helpful to guide future risk stratification.

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