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A systematic review of the efficacy of hydroxychloroquine in COVID-19 patients

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A Systematic Review of the Efficacy of Hydroxychloroquine in COVID-19 Patients

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Abstract

Hydroxychloroquine is a highly effective and commonly used disease-modifying anti-rheumatic drug (DMRD) for the treatment of various autoimmune diseases. Recently this medication received lot of attention in the medical world as a potential treatment for COVID-19. The goal of this research is to perform a systematic review of literature to focus on the efficacy of hydroxychloroquine in COVID-19 patients and any evidence of adverse reactions. The database used to conduct this research was PubMed, using four keywords and phrases: *effects*, *side effects*, *adverse events,* and *serious adverse events of hydroxychloroquine in COVID-19 patients*. Out of the 15 articles selected for the final review, 12 articles indicated no clinical improvement and 10 articles did not indicate any evidence of adverse reactions. The conclusion of the research is that hydroxychloroquine indicates lack of efficacy as treatment in patients with COVID-19, and there is not enough conclusive evidence for adverse reactions.

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Introduction

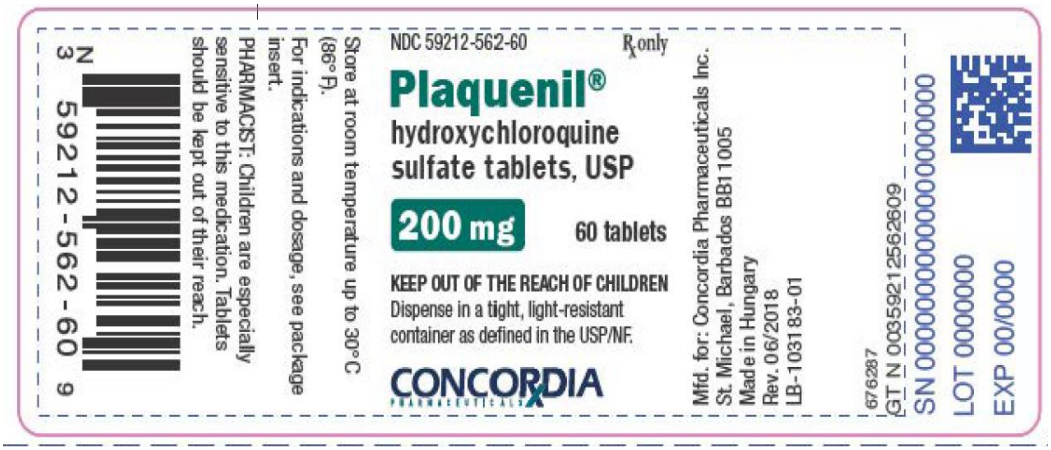
Hydroxychloroquine sulfate (also known as hydroxychloroquine and abbreviated as HCQ) is an antimalarial medicine approved in 1956 by the U.S. Food and Drug Administration (FDA, 2020a) for either prevention or treatment of certain types of malaria, lupus erythematosus, and rheumatoid arthritis. This drug belongs to the drug class called antimalarial quinolines or antirheumatics. It is a disease-modifying antirheumatic drug, also known as DMRD (Lupus Foundation of America, 2020). Currently, it is used to treat rheumatoid arthritis, some symptoms of lupus, childhood arthritis, and other autoimmune diseases (American College of Rheumatology, 2020). This drug is proven to be highly effective in reducing pain, stiffness, and inflammation associated with arthritis. It is believed that hydroxychloroquine interferes with the communication of cells in the immune system (American College of Rheumatology, 2020).

Hydroxychloroquine comes as an oral tablet with adult dosing ranging from 200 mg to 400 mg per day for rheumatic diseases and it needs a prescription. It is recommended to be taken with food. Symptoms can improve in one to two months, but it may take up to six months before the full benefits of this medication are experienced (American College of Rheumatology, 2020). Some of the common brand names of hydroxychloroquine are Plaquenil, Hydroquin, Axemal, and Dolquine, but Plaquenil is the most common brand. Hydroxychloroquine is in the World Health Organization's List of Essential Medicines (WHO, 2019), which shows the significance of hydroxychloroquine for the treatment of common autoimmune diseases. Antimalarials have been used to treat autoimmune diseases for years, and among them, hydroxychloroquine and chloroquine are often first-choice therapies. The efficacy of antimalarials is related to a strong modulation of the immune response as well as their photo protective properties (Rios-Fernandez,

2019). Due to its cost-effectiveness, safety, and efficacy hydroxychloroquine is especially used in rheumatic autoimmune disorders (RADs), such as rheumatoid arthritis, systemic lupus erythematosus, and primary Sjogren's syndrome (Nirk et al., 2020). The label for plaquenil, which is one of the popular brand names of hydroxychloroquine, is presented in Figure 1.

Figure 1

Label of Plaquenil



Note. An example of the label of Hydroxychloroquine sulfate (Plaquenil) from Concordia Pharmaceuticals Incorporation. Adapted from *GNH India.com*, 2021, Retrieved from https://www.gnhindia.com/products/us-ndc/hydroxychloroquine-sulfate-plaquenil-59212-562/. Copyright 2021 by GNH India.com.

In order to reiterate the significance of hydroxychloroquine for the treatment of autoimmune diseases, four major autoimmune disease states are evaluated and analyzed in comparison with most recent DMRDs. The four diseases chosen for this task are rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjogren's syndrome, and porphyria cutanea tarda (PCT).

Rheumatoid Arthritis

Rheumatoid Arthritis is a common, chronic, and systemic inflammatory autoimmune disease. The major treatments for rheumatoid arthritis currently are non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin and ibuprofen, and disease-modifying anti rheumatic drugs (DMRDs), like methotrexate and hydroxychloroquine. The newest classes of medications used to treat rheumatoid arthritis are called biological response modifiers, and they have been available for almost 10 years now (Gaffo et al., 2006). Some of the major biological agents that are used to treat RA are Infliximab, Adalimumab, and Etanercept (Gaffo et al., 2006). These agents act as human tumor necrosis factor alpha (TNF-α) inhibitors are designed to target the inflammatory mediators of tissue damage in rheumatoid arthritis (Gaffo et al., 2006). Even though the biological agents indicated similar efficacy results as the DMRDs, the efficacy of combination therapy is greater than monotherapy with either agent (Gaffo et al., 2006). Combination of DMRD therapy is generally well tolerated and a reasonable alternative to more expensive biological therapies (Gaffo et al., 2006). Even though there are several categories of treatments available currently, using DMRDs as monotherapy and as combination therapy depending on the severity of the disease is considered the first line treatment, and so hydroxychloroquine holds a significant role in the treatment of rheumatoid arthritis.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is the most common type of lupus. It is an autoimmune disease causing widespread inflammation and damage in the affected organs which predominantly affects women of childbearing age (D'Cruz, 2007). As an FDA-approved first-line indication, many people use hydroxychloroquine as an effective treatment. Not only has hydroxychloroquine been shown to prevent lupus flares, it also increases long-term survival of

patients with systemic lupus erythematosus (Husayn et al., 2020). It exhibits protective effects against lupus-associated organ damage, thrombosis, and bone density. In addition, hydroxychloroquine is also safe to use during pregnancy and breastfeeding. From 2001 to 2015, there was a rise in the proportion of women taking hydroxychloroquine during pregnancy due to safety studies suggesting a population in need of this drug (Husayn et al., 2020). According to the Lupus Foundation of America, no other drug provides similar broad benefits as hydroxychloroquine (Husayn et al., 2020). Quinacrine may be an alternative for patients with poor response or those who are intolerant to other antimalarials with the most frequent side effect of yellow skin discoloration (Rios-Fernandez, 2019). Among possible treatments for SLE, hydroxychloroquine comes as the first-line treatment because of its efficacy in treating autoimmune diseases.

Sjogren's Syndrome

Sjogren's syndrome is a chronic and very common autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates of the affected glands (Fox, 2005). The dryness of the eyes and mouth results from the involvement of the salivary and lacrimal glands (Fox, 2005). The exocrinopathy can be encountered alone as primary Sjogren's syndrome or in the presence of another autoimmune disorder such as rheumatoid arthritis, systemic lupus erythematosus, or progressive systemic sclerosis. (Fox, 2005). As treatment, the Sjogren's Syndrome Foundation (SSF) experts recommended a therapeutic step-by-step scheme that begins with hydroxychloroquine, and if the response is insufficient, methotrexate is indicated in the next step also in combination with hydroxychloroquine (Witte, 2019). If the first-line treatment is unsuccessful, other treatments like leflunomide, sulfasalazine, or azathioprine could be considered (Witte, 2019). Another reserve drug is cyclosporine, which can be used if the patient

does not respond to the other drug (Witte, 2019). In conclusion, hydroxychloroquine and a combination of hydroxychloroquine with methotrexate comes as the primary treatment for Sjogren's syndrome.

Porphyria Cutanea Tarda (PCT)

Porphyria cutanea tarda (PCT) is a disease of uroporphyrinogen decarboxylase inhibition, an enzyme involved in heme synthesis which eventually causes skin blisters (Husayn et al., 2020). Current treatment for PCT involves treatment with phlebotomy and hydroxychloroquine. Phlebotomy removes large quantities of blood, which removes iron, a substrate involved in heme synthesis. Hydroxychloroquine is an effective treatment strategy for PCT and may be superior to phlebotomy (Husayn et al., 2020). Low, oral doses of hydroxychloroquine 100 mg by mouth twice weekly reduces potential adverse effects while maintaining comparable safety and efficacy to phlebotomy (Husayn et al., 2020). Considering patient compliance, cost, and convenience, hydroxychloroquine is the reasonable option for patients with PCT (Husayn et al., 2020).

Based on the evaluation of above-mentioned disease states and the respective treatments, it is evident that there are not many alternate drugs in the market that are proven to be more effective and safer than hydroxychloroquine. Hydroxychloroquine is routinely prescribed to children with systemic lupus, and the side-effect profile is expected to be the same as adults (Chew, 2020). It is also advised that women with systemic lupus erythematosus or anti-Ro antibody-positive cutaneous lupus continue hydroxychloroquine during pregnancy when it is clinically indicated (Chew, 2020). All these facts indicate that hydroxychloroquine is well tolerated in pediatric patients and even during pregnancy. There are certain choices available for patients who cannot tolerate DMRDs, but hydroxychloroquine is considered as the primary treatment for many of the autoimmune disorders with proven safety and efficacy.

Background

The research involving hydroxychloroquine is highly significant at this point because of the recent use of this drug as a potential treatment for COVID-19. In March 2020, the FDA approved the Emergency Use Authorization (EUA) to use hydroxychloroquine to treat COVID-19 (FDA, 2020b). In June 2020, the FDA revoked the Emergency Use Authorization because it was determined that hydroxychloroquine is not an effective treatment for COVID-19 (FDA, 2020a). Millions of people took this drug during early 2020 as potential treatment for COVID-19 and resulted in a world-wide demand and shortage of supply. The subject for this research is so relevant at the time of this global pandemic since approval of hydroxychloroquine as potential treatment for COVID-19 was not based on evidence. It is a classic example of practice changing despite limited evidence to support its use. The use of hydroxychloroquine to treat COVID-19 patients was against the principles of evidence-based medicine. Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (Sackett et.al, 1996). The use of hydroxychloroquine in the face of the COVID-19 pandemic could be justified because both physicians and patients were scared, overwhelmed, and wanted fast answers. Another justification to use hydroxychloroquine as potential treatment for COVID-19 is that the traditional approach to validate a new treatment takes a long time.

The short-term and long-term side effects and adverse reactions caused by hydroxychloroquine in COVID-19 patients is still under evaluation and remains mostly unclear. Having an understanding on the reported adverse reactions of hydroxychloroquine in the current labeling will be beneficial prior to focusing on the adverse reactions caused by this drug in COVID-19 patients. As it was mentioned in the introduction, hydroxychloroquine is a commonly

used drug to treat many autoimmune diseases. The current labeling of hydroxychloroquine indicates a wide array of adverse reactions. Adverse drug reactions (ADR) are a major burden for patients, drug manufacturers and the healthcare industry because it is highly unpredictable. Early and accurate detection of potential ADRs can help to drug safety and reduce financial costs (Liu, 2019). Post-market spontaneous reports of ADRs remain a cornerstone for pharmacovigilance and a series of drug safety signal detection methods play an important role in providing drug safety insights. (Liu, 2019). The adverse reactions of hydroxychloroquine listed in the current labeling are presented in Table 1.

Table 1

Reported Adverse Reactions in the Current Labeling of Plaquenil

Adverse Reactions	Details
Blood and Lymphatic system disorders	Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.
Cardiac disorders	Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see WARNINGS and OVERDOSAGE). PLAQUENIL prolongs the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking PLAQUENIL (see OVERDOSAGE and DRUG INTERACTIONS).
Ear and Labyrinth disorders	Vertigo, tinnitus, nystagmus, nerve deafness, deafness.
Eye Disorders	Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, color vision abnormalities, corneal changes (edema and opacities) including corneal deposition of drug with or without accompanying symptoms (halo around lights, photophobia, blurred vision)
Gastrointestinal Disorders	Nausea, vomiting, diarrhea, and abdominal pain.
General disorders and administration site conditions	Fatigue.
Hepatobiliary disorders	Liver function tests abnormal, hepatic failure acute.
Immune system disorders	Urticaria, angioedema, bronchospasm
Metabolism and nutrition disorders	Decreased appetite, hypoglycemia, porphyria, weight decreased
Masculoskeletal and connective tissue disorders	Sensorimotor disorder, skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, depression of tendon reflexes and abnormal nerve conduction.
Nerveous system disorders	Headache, dizziness, seizure, ataxia and extrapyramidal disorders such as dystonia, dyskinesia, and tremor have been reported with this class of drugs.
Psychiatric disorders	Affect/emotional lability, nervousness, irritability, nightmares, psychosis, suicidal behavior.
Skin and subcutaneous tissue disorders	Rash, pruritus, pigmentation disorders in skin and mucous membranes, hair color changes, alopecia. Dermatitis bullous eruptions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, dermatitis exfoliative, acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although PLAQUENIL may precipitate attacks of psoriasis. It may be associated with pyrexia and hyperleukocytosis.

Note. Reported Adverse Reactions Listed in the Current Labeling of Plaquenil, Hydroxychloroquine sulfate tablets, U.S. Pharmacopeia. Adapted from *FDA.gov*, 2017, Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.

The most common cutaneous adverse reaction associated with hydroxychloroquine specified in the current labeling is skin pigmentation (Charfi et al., 2015). Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse induced by hydroxychloroquine

(Charfi et al., 2015). There are only 26 cases of hydroxychloroquine induced AGEP that were documented following a Medline search (Charfi et al., 2015). Based on Individual Case Safety Reports (ICSR) registered in Vigibase^{R} (1 January 2010 to 31 December 2019) according to Standardised MedDRA Queries (SMQs) classification, the main ADRs associated with hydroxychloroquine were hypersensitivity and allergic reactions, arthralgia, and skin disorders (Montastruc et al., 2020). Drug rash with eosinophilia and systemic symptoms (DRSS), acute generalized exanthematous pustulosis (AGEP), erythema multiforme, stevens-johnson syndrome, and toxic epidermal necrolysis have been reported associated with hydroxychloroquine (Chew, 2020). Adequate warnings from the physicians at the time of prescription will alert patients especially patients who take this treatment for the first time for any adverse reactions. It will allow the patients to cease the medication in a timely manner to stop any potential allergic reactions.

Another common adverse reaction in the current labeling is the well-known retinal toxicity caused by hydroxychloroquine after long-term use. Retinopathy is any damage to the retina of the eyes that can cause vision loss. Long-term treatment with hydroxychloroquine had been reported to cause severe irreversible retinal toxicity in susceptible individuals. According to Latasiewics (2017), hydroxychloroquine has now been shown to be associated with significant retinal toxicity. According to the same article, older studies have estimated hydroxychloroquine toxicity to be infrequent at around 0.5% to 1% of those taking hydroxychloroquine for greater than 5 years. Recent epidemiological data indicate that retinal toxicity occurs in greater than 10% of the patients who have taken hydroxychloroquine for over 10 years, and 20% to 50% of patients taking hydroxychloroquine for more than 20 years (Latasiewics, 2017). Studies show that retinal toxicity associated with hydroxychloroquine is an important problem with major

human and economic consequences ranging from blindness to the cost of screening (Wolfe & Marmor, 2010). Hydroxychloroquine retinopathy is of concern because of the potential seriousness of visual loss and the medicolegal consequences of failure to detect toxicity (Wolfe & Marmor, 2010). The risks associated with clinical parameters such as age, dose, cumulative dose, and duration of use will provide the tools for clinical societies to improve screening policies and guidelines and for individual physicians to make better judgement about the management of the disorder (Wolfe & Marmor, 2010).

The most interesting results based on the Individual Case Safety Reports (ICSR) were the relative high percent of cardiac ADRs (cardiomyopathy + arrhythmias = 8.3% of total ICSRs) showing that hydroxychloroquine first possess a myocardial toxicity, and second, can disturb cardiac rhythm (Montastruc et al., 2020). The fact that reported deaths were more than one out of three times from cardiac origin agrees with this conclusion. The present results show that the cardiac signal (QT prolongation and arrhythmias) found with hydroxychloroquine in COVID-19 patients were already present with rheumatoid arthritis and lupus (Montastruc et al., 2020).

There are several research studies indicating close association of hydroxychloroquine and cardiac adverse events not only in COVID-19 patients but also in patients with autoimmune disorders. According to Cohen et al. (2020), there was an increased reporting of cardiac adverse events in FDA Adverse Event Reporting System (FAERS) and its older version known as Adverse Event Reporting System (AERS) reports of chloroquine and hydroxychloroquine with respect to other therapeutics used for RA and SLE. This particular study analyzed 702,274 each of the FDA's adverse event reports which divided into chloroquine, hydroxychloroquine and control cohorts to determine their association with cardiac adverse events (Cohen et al., 2020). This study is indicating the connection of cardiac adverse events caused by hydroxychloroquine.

Based on the article “Cardiac Adverse Events Associated With Chloroquine and Hydroxychloroquine Exposure in 20 Years of Drug Safety Surveillance Reports,” in addition to the existing disease condition, other reasons like age, sex, and concurrent NSAID use were identified to contribute to cardiotoxicity reporting with hydroxychloroquine (Cohen et al., 2020).

Hydroxychloroquine was used to treat COVID-19 based on pre-existing in-vitro evidence of chloroquine and hydroxychloroquine reactions against viruses, specifically SARS-CoV2, made it a plausible option for COVID-19 (Edelman et al., 2020). This drug was an attractive choice for COVID-19 because not only did it show in-vitro evidence against the virus, but it also was already approved for other indications with well-documented safety profile and post market surveillance (Edelman et al., 2020). However due to accumulating data on the serious cardiac adverse events, the FDA determined the potential benefits no longer outweighed the risks of the medication. As it was mentioned earlier, on June 15, 2020, the FDA revoked the emergency use authorization for hydroxychloroquine in COVID-19 patients as the required legal criteria was no longer met.

Because of the increased number cardiac adverse events caused by this drug especially in COVID-19 patients, it was in the list of FDA Adverse Event Reporting System (FAERS) between April to June 2020, for further regulatory evaluation due to cardiotoxicity (FDA, 2020c). In critically ill COVID-19 patients, the risk of adverse cardiac events associated with the use of chloroquine and hydroxychloroquine is significantly high because of the impact on the myocardium due to cytokine storm from aggressive pulmonary infection and possible hypoxia in addition to the potential for viral myocarditis (Kamp et al., 2020). As of September 28, 2020, the status of hydroxychloroquine sulfate (plaquenil), chloroquine phosphate, and generic products

containing hydroxychloroquine and chloroquine, are evaluated by the FDA for the need of any regulatory action (FDA, 2020c).

Since hydroxychloroquine is still considered as a significant treatment for autoimmune diseases, it is important to focus on the efficacy of this drug in COVID-19 patients, especially when it was used on patients without data from clinical trials. The purpose of this research is to conduct a systematic review of literature for evidence of efficacy of hydroxychloroquine in COVID-19 patients based on results from clinical trials. In addition, the study will also focus on any evidence of adverse reactions reported in patients as a result of using hydroxychloroquine as treatment for COVID-19.

Methods

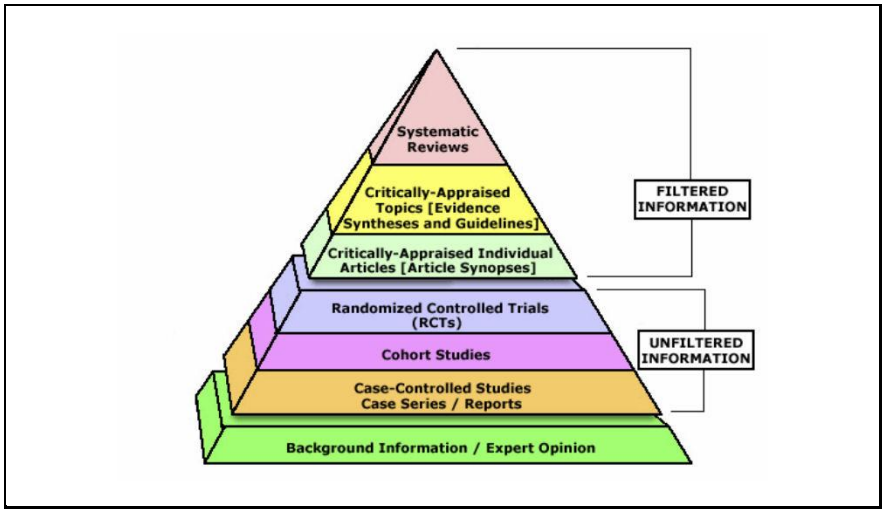
The method that was used to conduct this research project was a systematic review of literature based on clinical trials that focused on the efficacy of hydroxychloroquine in COVID-19 patients. Systematic reviews and meta-analyses are being increasingly used to summarize medical literature and identify areas in which research is needed (Crowther & Lim, 2010). Systematic reviews limit bias with the use of reproducible scientific process to search the literature and evaluate the quality of the individual studies, and if possible, results are statistically combined into meta-analyses in which the data is weighted and pooled to produce an estimate of effect (Crowther & Lim, 2010). A meta-analysis is a statistical study that combines the result of several scientific studies on the topic. It is a quantitative, formal and epidemiological study design used to systematically assess the results of previous research to drive conclusions about the body of the research (Haidich, 2010). Outcomes from a meta-analysis may include a precise estimate of the effect of treatment, or risk factor for disease, or other outcomes than any individual study contributing to the pooled analysis (Haidich, 2010). Since the results gathered for the purpose of writing this thesis is qualitative than quantitative, the meta-analyses part is not that significant compared to systematic review.

As per Crowther and Lim (2010), the inferences made from systematic reviews are usually evidence based. As it is indicated in Figure 2, the quality of evidence derives from observational studies, experimental studies, and critical appraisal. The search for evidence is mainly using electronic databases like PubMed, MEDLINE, Embase, and Cochrane Library. The completeness of the search strategy will determine the comprehensiveness of the review (Crowther & Lim, 2010). Apart from the above mentioned electronic databases, many other sources like registers of clinical trials (www.clinicaltrials.gov), data clearing houses

(www.guideline.gov) and agencies like FDA and CDC (www.FDA.gov and www.CDC.gov) could be used for literature review.

Figure 2

Quality of Evidence Pyramid



Note. The Evidence Based Medicine Pyramid. Adapted from *cochrane.org*, by D. Minkow, 2014, Retrieved from https://s4be.cochrane.org/blog/2014/04/29/the-evidence-based-medicine-pyramid/. Copyright 2021 by Students 4 Best Evidence.

For the purpose of conducting this research, the main source of literature review is PubMed. The reason the search was limited to only one electronic database was to control the enormous search results related to hydroxychloroquine because of the pandemic. Published literature from sources other than PubMed and websites of agencies and foundations, especially the U.S. Food and Drug Administration, were also used to gather evidence for this research. The studies selected for the literature review were chosen from PubMed published between October 2020 and September 2021. The text-availability filter was selected for abstract, and the article-type filter was selected for clinical trial and randomized controlled trial. The publication date selected was for one year. The summary for the search filters is given in table format in Table 2.

Table 2

Search Filters Used in PubMed

PubMed.gov	Selected Filters
Text Availability	Abstract
Article Type	Clinical Trial and Randomized Controlled Trial
Publication Date	1 Year

The search on PubMed was conducted using four key words as *effects, side effects*, *adverse events* and *serious adverse events* of *hydroxychloroquine in COVID-19 patients.* The articles were evaluated based on the inclusion and exclusion criteria established and specified below. The abstracts were reviewed for all articles and categorized based on the primary and secondary outcome presented below. The elimination of studies was based on multiple reasons such as duplicate, not relevant, no abstract available and not based on clinical trials. A PRISMA flowchart is presented with details of the selection process is presented in Figure 3. The selected studies were further categorized into type of study, primary outcome, and secondary outcome in COVID-19 patients. A summary of all the selected studies is presented in the Appendix.

Inclusion Criteria

Studies satisfying the following criteria were included in the analysis:

- articles published within one year (between October 2020 and September 2021),
- samples which included COVID-19 patients,
- studies based on only clinical trials and randomized controlled trials, and
- abstracts that specifically addressed the primary and secondary outcomes for the search.

Exclusion Criteria

Any study that had one of the following criteria were excluded:

- articles published before October 2020,

- studies based on any other methods except clinical trial and randomized controlled clinical trial,
- abstracts that did not address the primary and secondary outcome for the search,
- articles that did not directly address the issues of COVID-19 patients, and
- articles in any other languages other than English.

Primary Outcome

- Evidence for any clinical improvement of symptoms of COVID-19 patients by using hydroxychloroquine.

Secondary Outcome

- Signs of adverse events caused specifically by hydroxychloroquine in COVID-19 patients.
- Signs of serious adverse events caused specifically by hydroxychloroquine in COVID-19 patients.
- Reported adverse events of hydroxychloroquine with any other combination drugs in COVID-19 patients.

Results

The results for the initial search are presented in a table format for each keyword (see Table 3). The search results were further screened based on the inclusion and exclusion criteria, and the results are presented in a flow chart format (see Figure 3). The articles selected for final evaluation were based on the primary and secondary outcomes mentioned in the methods section.

Table 3

Results of Keyword Search

Key Words	Number of Publications (PubMed) October 2020-September 2021	Total Number of Publications (PubMed)
Effects of hydroxychloroquine in COVID-19 patients	44	
Side Effects of hydroxychloroquine in COVID-19 patients	20	
Adverse Events of hydroxychloroquine in COVID-19 patients	12	
Serious Adverse of Events of hydroxychloroquine in COVID-19 patients	5	
Articles found by citation matching	7	88

An overall summary of the study selection process is presented in Table 4.

Table 4

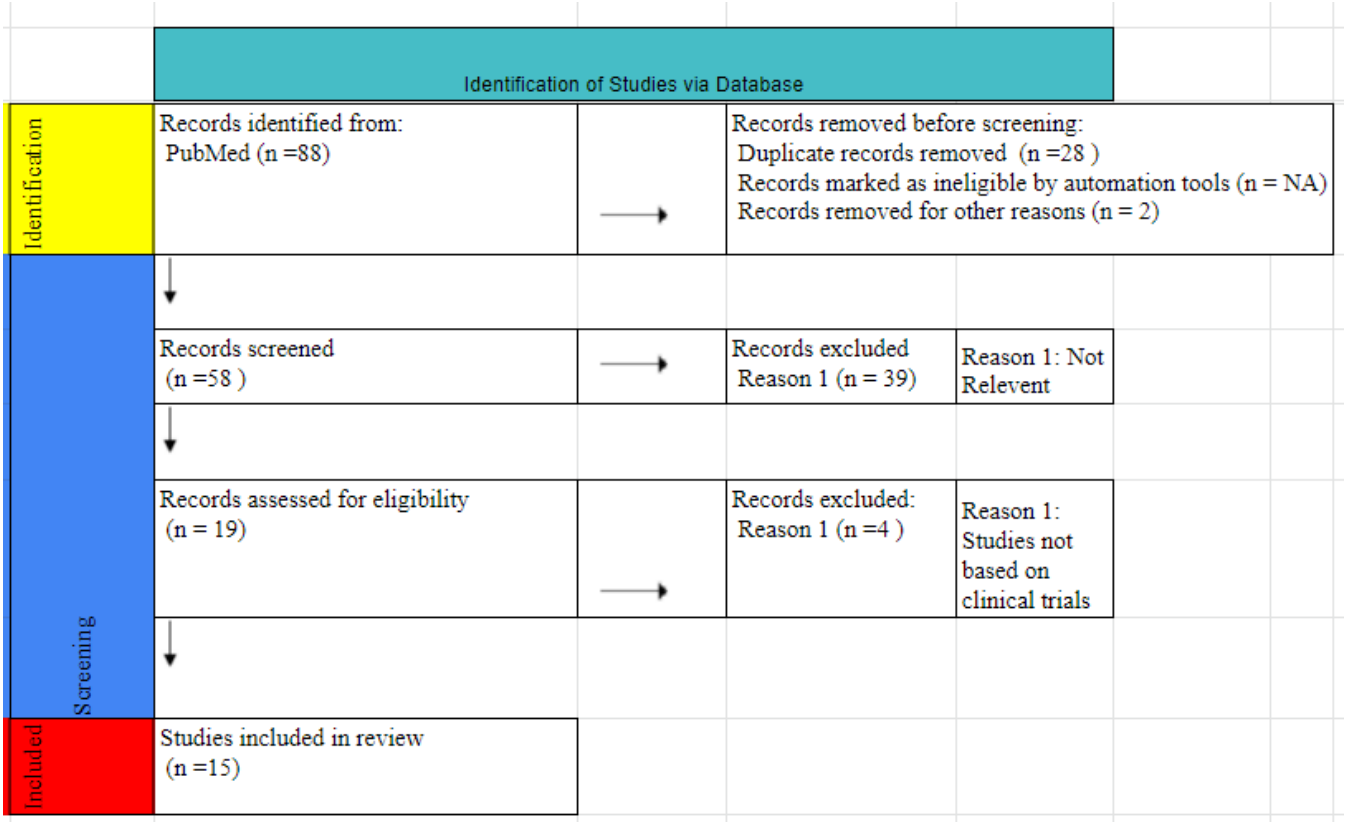
Summary of Study Selection Method

Summary of Study Selection Method	Number of Studies
Selected	15
Duplicate	28
Not Relevant	39
No Abstract Available	2
Not Based on Clinical Trial	4

A flowchart with details of the selection process is depicted in the Figure 3.

Figure 3

Flowchart for the Study Selection Process



Once the 15 studies were selected for the final evaluation, each study was reviewed for the primary outcome and secondary outcomes specified in the methods section. The results were summarized on an Excel spreadsheet and are presented on the Appendix at the end of the thesis. Out of 15 articles selected, only three articles showed any evidence of potential effects of hydroxychloroquine, and 12 of the articles indicated the primary outcome as no clinical improvement confirming lack of efficacy of hydroxychloroquine in COVID-19 patients when used as treatment. The summary of the primary outcome is presented in Table 5 and Table 6. For the evaluation of secondary outcome, all 15 articles were reviewed for signs of adverse reactions caused by hydroxychloroquine in COVID-19 patients. Out of 15 articles, 10 articles did not indicate any evidence of adverse reactions caused by hydroxychloroquine in COVID-19 patients. The remaining five articles indicated some evidence of adverse reactions in which some are specifically addressing cardiac failure. The results of the secondary outcome are presented in Table 7 and Table 8.

Table 5

Summary of Studies Indicating Evidence of Primary Outcome

Citation	Title of the Selected Articles	Type of Study	Primary Outcome
Abbas et al., 2021	Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A natural clinical trial	Clinical Trial	Reduced signs and symptoms significantly
Dabbous et al., 2021	Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial	Randomized Controlled Trial	Favipiravir could be used as an alternative for hydroxychloroquine
Arabi et al., 2021	Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial	Randomized, Controlled Clinical Trial	Worsened outcome compared to no antiviral therapy

Table 6

Summary of Studies Indicating No Evidence of Primary Outcome

Citation	Title of the Selected Articles	Type of Study	Primary Outcome
Recovery Collaborative Group, 2020	Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19	Randomized Controlled Trial	No Clinical Improvement
Mitja et al., 2021	A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19	Cluster-Randomized Trial	No Clinical Improvement
WHO Solidarity Trial Consortium et al., 2021	Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results	Randomized Controlled Trial	No Clinical Improvement
Skipper et al., 2020	Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial	Randomized Controlled Trial	No Clinical Improvement
Furtado et al., 2020	Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial	Randomized Controlled Trial	No Clinical Improvement
Chen et al., 2020	A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19)	Randomized Controlled Trial	No Clinical Improvement
Abella et al., 2021	Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial	Randomized, double blind, Placebo-Controlled Trial	No Clinical Improvement
Schwartz et al., 2021	Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial	Randomized Controlled Trial	No Clinical Improvement
Reis et al., 2021	Effect of Early Treatment with Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial	Randomized Clinical Trial	No Clinical Improvement
Galan et al., 2021	Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection	Randomized, double blinded, Phase 2 Trial	No Clinical Improvement
Self et al., 2020	Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial	Randomized, Blinded, Placebo-Controlled, Multi-center Trial	No Clinical Improvement
Lyngbakken et al., 2020	A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics	Pragmatic, Randomized, Controlld Trial	No Clinical Improvement

Table 7

Summary of Studies Indicating No Evidence of Secondary Outcome

Citation	Title of the Selected Articles	Type of Study	Secondary Outcome
WHO Solidarity Trial Consortium et al., 2021	Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results	Randomized Controlled Trial	No evidence of adverse reactions mentioned in the article
Skipper et al., 2020	Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial	Randomized Controlled Trial	No evidence of adverse reactions mentioned in the article
Furtado et al., 2020	Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial	Randomized Controlled Trial	No evidence of adverse reactions mentioned in the article
Chen et at., 2020	A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19)	Randomized Controlled Trial	No evidence of adverse reactions mentioned in the article
Abella et al., 2021	Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial	Randomized, double blind, Placebo-Controlled Trial	No evidence of adverse reactions mentioned in the article
Schwartz et al., 2021	Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial	Randomized Controlled Trial	No evidence of adverse reactions mentioned in the article
Reis et al., 2021	Effect of Early Treatment with Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial	Randomized Clinical Trial	No evidence of adverse reactions mentioned in the article
Galan et al., 2021	Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection	Randomized, double blinded, Phase 2 Trial	No evidence of adverse reactions mentioned in the article
Self et al., 2020	Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial	Randomized, Blinded, Placebo-Controlled, Multi-center Trial	No evidence of adverse reactions mentioned in the article
Lyngbakken et al., 2020	A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics	Pragmatic, Randomized, Controlld Trial	No evidence of adverse reactions mentioned in the article

Table 8

Summary of Studies Indicting Evidence of Secondary Outcome

Citation	Title of the Selected Articles	Type of Study	Secondary Outcome
Recovery Collaborative Group, 2020	Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19	Randomized Controlled Trial	Invasive Mechanical Ventilation, Cardiac Death
Mitja et al., 2021	A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19	Cluster-Randomized Trial	Higher Adverse reactions, No Serious Adverse reaction
Abbas et al., 2021	Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A natural clinical trial	Clinical Trial	Side effects related to heart rythum
Dabbous et al., 2021	Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial	Randomized Controlled Trial	Acute Myocarditis, Acute heart failure
Arabi et al., 2021	Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial	Randomized, Controlled Clinical Trial	Evidence of Mild Adverse Events

As a result of the literature review done on the efficacy of hydroxychloroquine in COVID-19 patients, 80% of the articles indicated no evidence of clinical improvement, and only 20% articles indicated effects of hydroxychloroquine in patients with COVID-19. For the secondary outcome of signs of adverse reactions, 66.7% of the articles indicated no evidence of adverse reactions, and 33.3% articles indicated signs of adverse reactions. The summary of the results is presented in Table 9.

Table 9

Summary of Results in Percent

Summary of Results	% of Articles
Evidence of Primary Outcome (Clinical Improvement)	20
No Evidence of Primary Outcome (Clinical Improvement)	80
Evidence of Secondary Outcome (Adverse Reactions)	33.3
No Evidence of Secondary Outcome (Adverse Reaction)	66.7

As it is presented in Table 9, majority of the articles did not indicate any evidence of efficacy of hydroxychloroquine in COVID-19 patients. As for the secondary outcome of signs of adverse reactions, majority of the selected articles did not indicate any evidence of adverse reactions. Because this is a review of literature, there were not enough conclusive evidence to state that there is no efficacy for hydroxychloroquine or there are no adverse reactions caused by hydroxychloroquine in patients with COVID-19. These results are only based on the articles that were selected for this particular research. The results are discussed in detail in the discussion section.

Discussion

For the systematic review of literature to evaluate the efficacy of hydroxychloroquine in COVID-19 patients, 15 studies were selected for the final review. All the selected studies for the literature review were based on clinical trials or randomized controlled clinical trials. Out of fifteen selected studies, the primary outcome for twelve studies indicated no clinical improvement caused by hydroxychloroquine in COVID-19 patients (refer to Table 6). One specific study indicated reduction of signs and symptoms significantly (Abbas et al., 2021), and another study indicated worsened outcome compared to no antiviral therapy (Arabi et al., 2021). One study indicated favipiravir as a possible alternative for hydroxychloroquine for the treatment of COVID-19 (Dabbous et al., 2021). Based on the literature review of the 15 articles selected for this research, it is concluded that there was no clinical improvement using hydroxychloroquine in COVID-19 patients. The lack of efficacy of hydroxychloroquine for the treatment of COVID-19 is evident from the results of the literature review. The conclusion agrees with the fact that the FDA revoked the emergency use authorization for the use of hydroxychloroquine in COVID-19 patients due to lack of improvement on the symptoms.

For the evaluation of the secondary outcome, all 15 studies were reviewed for any evidence of adverse reactions reported in COVID-19 patients as a result of using hydroxychloroquine as a treatment. Ten studies did not mention any evidence of adverse reactions (refer to Table 7), and five studies indicated evidence of adverse reactions mostly related to heart failure. The article titled as “Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19” indicated invasive mechanical ventilation and cardiac death as the adverse reactions caused by hydroxychloroquine (Recovery Collaborative Group, 2020). According to Abbas et al. (2021), the adverse reactions were associated with heart rhythm. Acute myocarditis and acute heart failure are also recorded as adverse reactions based on article titled

as “Safety and Efficacy of Favipiravir Versus Hydroxychloroquine in Management of COVID-19: A Randomised Controlled Trial” (Dabbous et al., 2021). There were two studies mentioning evidence of adverse events in general without specific details, caused by hydroxychloroquine in COVID-19 patients (Mitja et al., 2021; Arabi et al., 2021). The results from the literature review do not have enough evidence for any strong conclusion regarding adverse reactions of hydroxychloroquine in COVID-19 patients. Because the selected studies for this research do not indicate any conclusive evidence of adverse reactions caused by hydroxychloroquine in COVID-19 patients, the subject is discussed in detail with more evidence from recently published studies.

The most common reported adverse reaction of hydroxychloroquine in COVID-19 patients is prolonged QT interval which predisposes to ventricular tachycardia (Pareek et al., 2020). QT interval is measured on electrocardiogram which is used to assess some of the electrical properties of the heart. The primary concern with short term, high dose 4-aminoquinoline regimen is cardiovascular toxicity (Recovery Collaborative Group, 2020). Corona virus disease (COVID-19) is a pro-arrhythmogenic state created by direct viral myocardial damage, hypoxia, hypotension, enhanced inflammatory status, electrolyte abnormalities, concomitant QT-prolongation medications, and underlying cardiovascular diseases, with the risk of being higher in patients with severe COVID-19 (Pareek et al., 2020).

Combined use of hydroxychloroquine and azithromycin was also adopted globally to treat COVID-19 patients. Studies indicate that this combination also results in significant QT prolongation in approximately one in four hospitalized patients. The degree of QT prolongation is severe, exceeding 500 milliseconds in 14% of patients and resulting in a case of Torsades de Pointes (Maraj et al., 2020). Torsades de Pointes is considered as one of several types of life-threatening heart rhythm disturbances. Based on these studies, it is evident that

hydroxychloroquine and the combination of hydroxychloroquine with azithromycin could trigger cardiac failures in patients with COVID-19.

Studies indicated that COVID-19 patients could be more susceptible to adverse reactions caused by hydroxychloroquine because of the compromised functions of the vital organs caused by COVID-19 infection. Since hydroxychloroquine is cleared by the kidney and the liver, patients who are highly sick particularly ones with impaired renal or hepatic functions, are at increased risk of experiencing serious adverse reactions (Younis et al., 2020). Drug-drug interactions are also a major cause of adverse reactions associated with hydroxychloroquine (Younis et al., 2020). Additionally, there were several other non-life-threatening side effects like diarrhea, non-specific abdominal pain, dyspepsia, bloating, nausea, vomiting, headache, skin rash, insomnia, dizziness, fatigue, and blurred vision, etc, observed in COVID-19 patients as a result of the use of hydroxychloroquine.

Based on the adverse reactions listed on the package insert and recent studies published, the suggested warning at the time of prescription that could be beneficial to the patients are mainly for retinal toxicity and cardiotoxicity. Recent studies in COVID-19 patients indicated that hydroxychloroquine could cause blurred vision in some patients. Even though retinal toxicity is caused by prolonged use of hydroxychloroquine, doctors should warn about this and explain the seriousness of this side effect at the time of prescription so that patients could be aware of it and could consult with the ophthalmologist for regular monitoring. Ophthalmologists, rheumatologists, and general practitioners should be aware of the best practices in safe prescribing of hydroxychloroquine and any consensus criteria to ensure those who require screening for hydroxychloroquine retinopathy are appropriately referred (Yusuf, 2017).

Recommendation for Future Research

Based on the evaluation of the articles with the adverse drug reactions associated with hydroxychloroquine, it can be concluded that additional research was mostly done in the area of cardiac ADRs and retinal toxicity. There was not much evidence collected in terms of additional research around allergic reactions caused by hydroxychloroquine. With the COVID-19 situation, a lot of research has been done and is in process around QT prolongation and cardiac arrhythmia. Several studies have been conducted to investigate cardiotoxicity associated with hydroxychloroquine usage in both non-Covid and Covid-infected patients. A total of 3,237 studies are currently registered at the U.S. National Institute of Health's National Library of Medicine portal from 114 countries, of which 793 are investigating various treatment options in Copvid-19 (Raza et al., 2021). Among these, a total of 68 studies refer to hydroxychloroquine usage in COVID-19 (Raza et al., 2021). Based on the research that was used to write this thesis, it is recommended that additional research about cardiac adverse reactions and allergic reactions associated with hydroxychloroquine use will also be beneficial to patients at the time of prescription.

Limitation of the Study

The primary limitation of this thesis was the limited number of databases used for the keyword search as the studies were only included from PubMed. Another limitation was the type of study chosen to include in the literature review as it only included clinical trials and randomized clinical trials.

Conclusion

The global pandemic known as COVID-19 brought hydroxychloroquine to the forefront of the medical world and to the research community as a potential treatment for COVID-19, but without the support of clinical data. Even though there was not much research done on this medicine nor any major regulatory updates done since the approval, a lot of research studies have been done already or are in process due to the use of this medicine as potential treatment in the early stages of the pandemic. The conclusion of this research study based on the literature review and analysis is that there is no evidence of clinical improvement caused by hydroxychloroquine in COVID-19 patients. Based on this study, there are no conclusive evidence for any signs of adverse reactions in patients with COVID-19 as a result of using hydroxychloroquine as treatment. The conclusion of this research confirms the FDA's decision to revoke the emergency use authorization as there is lack of evidence for clinical improvement. Additional research is highly recommended in the areas of cardiotoxicity and cutaneous adverse reactions in order to minimize the consequences of severe adverse reactions caused by hydroxychloroquine in patients.

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Appendix: List of Articles Used for Final Review

Title of the Selected Articles	Type of Study	Primary Outcome on COVID-19 patients	Secondary Outcome on COVID-19 Patients	Citation
Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19	Randomized Controlled Trial	No Clinical Improvement	Invasive Mechanical Ventilation, Cardiac Death	RECOVERY Collaborative Group, Horby, P., Mafham, M., Linsell, L., Bell, J. L., Staplin, N., Emberson, J. R., Wiselka, M., Ustianowski, A., Elmahi, E., Prudon, B., Whitehouse, T., Felton, T., Williams, J., Faccenda, J., Underwood, J., Baillie, J. K., Chappell, L. C., Faust, S. N., Jaki, T., … Landray, M. J. (2020). Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19. The New England journal of medicine, 383(21), 2030–2040. https://doi.org/10.1056/NEJMoa2022926
A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19	Cluster-Randomized Trial	No Clinical Improvement	Higher Adverse reactions, No Serious Adverse reaction	Mitjà, O., Corbacho-Monné, M., Ubals, M., Alemany, A., Suñer, C., Tebé, C., Tobias, A., Peñafiel, J., Ballana, E., Pérez, C. A., Admella, P., Riera-Martí, N., Laporte, P., Mitjà, J., Clua, M., Bertran, L., Sarquella, M., Gavilán, S., Ara, J., Argimon, J. M., … BCN-PEP-CoV2 Research Group (2021). A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19. The New England journal of medicine, 384(5), 417–427. https://doi.org/10.1056/NEJMoa2021801
Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A natural clinical trial	Clinical Trial	Reduced signs and symptoms significantly	Side effects related to heart rythum	Abbas, H. M., Al-Jumaili, A. A., Nassir, K. F., Al-Obaidy, M. W., Al Jubouri, A. M., Dakhil, B. D., Abdulelah, M. M., & Al Khames, Q. A. (2021). Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A natural clinical trial. International journal of clinical practice, 75(4), e13856. https://doi.org/10.1111/ijcp.13856
Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial	Randomized Controlled Trial	favipiravir could be used as an alternative for hydroxychloroquine	Acute Myocarditis, Acute heart failure	Dabbous, H. M., El-Sayed, M. H., El Assal, G., Elghazaly, H., Ebeid, F., Sherief, A. F., Elgaafary, M., Fawzy, E., Hassany, S. M., Riad, A. R., & TagelDin, M. A. (2021). Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. Scientific reports, 11(1), 7282. https://doi.org/10.1038/s41598-021-85227-0
Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results	Randomized Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	WHO Solidarity Trial Consortium, Pan, H., Peto, R., Henao-Restrepo, A. M., Preziosi, M. P., Sathiyamoorthy, V., Abdool Karim, Q., Alejandria, M. M., Hernández García, C., Kieny, M. P., Malekzadeh, R., Murthy, S., Reddy, K. S., Roses Periago, M., Abi Hanna, P., Ader, F., Al-Bader, A. M., Alhasawi, A., Allum, E., Alotaibi, A., … Swaminathan, S. (2021). Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine, 384(6), 497–511. https://doi.org/10.1056/NEJMoa2023184
Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial	Randomized Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Skipper, C. P., Pastick, K. A., Engen, N. W., Bangdiwala, A. S., Abassi, M., Lofgren, S. M., Williams, D. A., Okafor, E. C., Pullen, M. F., Nicol, M. R., Nascene, A. A., Hullsiek, K. H., Cheng, M. P., Luke, D., Lother, S. A., MacKenzie, L. J., Drobot, G., Kelly, L. E.,

				Schwartz, I. S., Zarychanski, R., … Boulware, D. R. (2020). Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. Annals of internal medicine, 173(8), 623–631. https://doi.org/10.7326/M20-4207
Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial	Randomized Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Furtado, R., Berwanger, O., Fonseca, H. A., Corrêa, T. D., Ferraz, L. R., Lapa, M. G., Zampieri, F. G., Veiga, V. C., Azevedo, L., Rosa, R. G., Lopes, R. D., Avezum, A., Manoel, A., Piza, F., Martins, P. A., Lisboa, T. C., Pereira, A. J., Olivato, G. B., Dantas, V., Milan, E. P., … COALITION COVID-19 Brazil II Investigators (2020). Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet (London, England), 396(10256), 959–967. https://doi.org/10.1016/S0140-6736(20)31862-6
A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19)	Randomized Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Chen, C. P., Lin, Y. C., Chen, T. C., Tseng, T. Y., Wong, H. L., Kuo, C. Y., Lin, W. P., Huang, S. R., Wang, W. Y., Liao, J. H., Liao, C. S., Hung, Y. P., Lin, T. H., Chang, T. Y., Hsiao, C. F., Huang, Y. W., Chung, W. S., Cheng, C. Y., Cheng, S. H., & Taiwan HCQ Study Group (2020). A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). PloS one, 15(12), e0242763. https://doi.org/10.1371/journal.pone.0242763
Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial	Randomized, double blind, Placebo- Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Abella, B. S., Jolkovsky, E. L., Biney, B. T., Uspal, J. E., Hyman, M. C., Frank, I., Hensley, S. E., Gill, S., Vogl, D. T., Maillard, I., Babushok, D. V., Huang, A. C., Nasta, S. D., Walsh, J. C., Wiletyo, E. P., Gimotty, P. A., Milone, M. C., Amaravadi, R. K., & Prevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators (2021). Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial. JAMA internal medicine, 181(2), 195–202. https://doi.org/10.1001/jamainternmed.2020.6319
Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial	Randomized Controlled Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Schwartz, I., Boesen, M. E., Cerchiaro, G., Doram, C., Edwards, B. D., Ganesh, A., Greenfield, J., Jamieson, S., Karnik, V., Kenney, C., Lim, R., Menon, B. K., Mponponsuo, K., Rathwell, S., Ryckborst, K. J., Stewart, B., Yaskina, M., Metz, L., Richer, L., Hill, M. D., … ALBERTA HOPE COVID-19 Collaborators (2021). Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial. CMAJ open, 9(2), E693–E702. https://doi.org/10.9778/cmajo.20210069

Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial	Randomized Clinical Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Reis, G., Moreira Silva, E., Medeiros Silva, D. C., Thabane, L., Singh, G., Park, J., Forrest, J. I., Harari, O., Quirino Dos Santos, C. V., Guimarães de Almeida, A., Figueiredo Neto, A. D., Savassi, L., Milagres, A. C., Teixeira, M. M., Simplicio, M., Ribeiro, L. B., Oliveira, R., Mills, E. J., & TOGETHER Investigators (2021). Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA network open, 4(4), e216468. https://doi.org/10.1001/jamanetworkopen.2021.6468
Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection	Randomized, double blinded, Phase 2 Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Galan, L., Santos, N., Asato, M. S., Araújo, J. V., de Lima Moreira, A., Araújo, A., Paiva, A., Portella, D., Marques, F., Silva, G., de Sousa Resende, J., Tizolim, M. R., Santos, P. L., Buttenbender, S. F., de Andrade, S. B., Carbonell, R., Da Rocha, J. G., de Souza, R., & da Fonseca, A. J. (2021). Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathogens and global health, 115(4), 235–242. https://doi.org/10.1080/20477724.2021.1890887
Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial	Randomized, Blinded, Placebo-Controlled, Multi-center Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Self, W. H., Semler, M. W., Leither, L. M., Casey, J. D., Angus, D. C., Brower, R. G., Chang, S. Y., Collins, S. P., Eppensteiner, J. C., Filbin, M. R., Files, D. C., Gibbs, K. W., Ginde, A. A., Gong, M. N., Harrell, F. E., Jr, Hayden, D. L., Hough, C. L., Johnson, N. J., Khan, A., Lindsell, C. J., … Diercks, D. (2020). Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA, 324(21), 2165–2176. https://doi.org/10.1001/jama.2020.22240
A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics	Pragmatic, Randomized, Controlld Trial	No Clinical Improvement	No evidence of adverse reactions mentioned in the article	Lyngbakken, M. N., Berdal, J. E., Eskesen, A., Kvale, D., Olsen, I. C., Rueegg, C. S., Rangberg, A., Jonassen, C. M., Omland, T., Røsjø, H., & Dalgard, O. (2020). A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nature communications, 11(1), 5284. https://doi.org/10.1038/s41467-020-19056-6
Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial	Randomized, Controlled Clinical Trial	Worsened Outcome compared to no antiviral therapy	Evidence of Mild Adverse Events	Arabi, Y. M., Gordon, A. C., Derde, L., Nichol, A. D., Murthy, S., Beidh, F. A., Annane, D., Swaidan, L. A., Beane, A., Beasley, R., Berry, L. R., Bhimani, Z., Bonten, M., Bradbury, C. A., Brunkhorst, F. M., Buxton, M., Buzgau, A., Cheng, A., De Jong, M., Detry, M. A., … REMAP-CAP Investigators (2021). Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial. Intensive care medicine, 47(8), 867–886. https://doi.org/10.1007/s00134-021-06448-5