Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Hydroxychloroquine

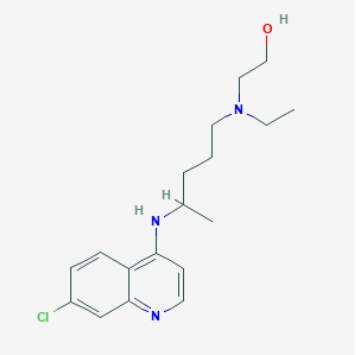
Evidence Summary

Hydroxychloroquine improves metabolic and cardiovascular profiles but has failed to improve cognitive functions. Long-term high-dose treatment can result in serious irreversible cardiac and retinal damage.

Neuroprotective Benefit: Clinical trials have failed to demonstrate improvement in cognitive functions with hydroxychloroquine treatment in patients with Alzheimer's disease or Lyme disease. Hydroxychloroquine can induce neuropsychiatric events.

Aging and related health concerns: Hydroxychloroquine treatment decreases the risk of cardiovascular disease and metabolic dysfunctions in patients with rheumatic diseases. Addition of hydroxychloroquine may also increase response rate and survival in some late-stage cancer patients.

Safety: Long-term high-dose treatment may result in serious irreversible damage, such as retinopathy and cardiac toxicity, including cardiac failure and death. Hydroxychloroquine use during pregnancy may increase the risk for spontaneous abortions.

Availability: Rx.	**Dose**: 200 to 400 mg daily for rheumatoid arthritis and lupus erythematosus, (Drugs.com); 400 mg once weekly for the prophylaxis of malaria (Drugs.com)	**Chemical formula:** $C_{18}H_{28}ClN_3O$ **MW**: 335.9  Source: PubChem
Half life: absorption half-life of 3-4 hours; half-life of 22.4 days in blood. IV dose has half-life of 40 days.	**BBB**: penetrant; can achieve concentrations 10-20 times greater than plasma concentrations.	
Clinical trials: Randomized controlled trials have enrolled several hundred patients with diabetes, arthritis, etc.	**Observational studies**: The largest meta-analysis of 19 observational studies included 19,679 subjects with rheumatic disease.	

What is it? Hydroxychloroquine is a synthetic anti-malarial drug that is also used for the treatment of rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, Sjögren's syndrome, and dermatomyositis (Mascolo et al., 2019). Hydroxychloroquine is also used for the prophylaxis of malaria. The exact mechanisms of hydroxychloroquine are unknown, though there are numerous mechanisms hypothesized for different indications. Hydroxychloroquine accumulates in the lysosomes of the malaria parasite, raising the pH of the vacuole, interfering with the parasite's ability to proteolyze hemoglobin and preventing the normal growth and replication of the parasite (DrugBank.ca).

Hydroxychloroquine accumulation in human organelles also raise their pH, inhibiting antigen processing, and preventing the alpha and beta chains of the major histocompatibility complex class II from dimerizing, leading to the inhibition of antigen presentation and a reduced inflammatory response (DrugBank.ca). Elevated pH in the vesicles can result in only the high affinity complexes to be presented on the cell surface. Hydroxychloroquine may reduce the release of cytokines such as IL-1 and TNF.

Hydroxychloroquine and chloroquine are both being investigated for the treatment of COVID-19. The raised pH in endosomes is thought to prevent virus particles from utilizing their activity for fusion and entry into the cell (Owens, 2020). Based on *in vitro* work, hydroxychloroquine inhibits terminal glycosylation of ACE2, the receptor that COVID-19 targets for cell entry (DrugBank.ca).

Neuroprotective Benefit: Clinical trials have failed to demonstrate improvement in cognitive functions with hydroxychloroquine treatment in patients with Alzheimer's disease or Lyme disease. Hydroxychloroquine can induce neuropsychiatric events.

Types of evidence:

- 3 clinical trials (1 RCT in Alzheimer's patients, 1 pilot study in Alzheimer's patients, 1 RCT in Lyme disease patients)
- 2 observational studies
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical studies have tested whether hydroxychloroquine can prevent cognitive decline or dementia.

In a randomized controlled trial of 239 patients with Lyme disease-attributed persistent symptoms, intravenous ceftriaxone followed by a 12-week blinded oral regimen of doxycycline, clarithromycin/hydroxychloroquine, or placebo did not result in neuropsychological and cognitive measures that were different across groups (Berende et al., 2019). After 14 weeks, none of the cognitive domain scores differed significantly between the treatment arms. At follow-up, no additional treatment effect or difference between groups emerged at any time point.

In an observational study of 123 patients with systemic lupus erythematosus, hydroxychloroquine use was not significantly associated with cognitive performance (McLaurin et al., 2005).

Human research to suggest benefits to patients with dementia:

In a double-blind randomized controlled trial of 168 early Alzheimer's patients, hydroxychloroquine treatment (200 or 400 mg, dependent on body weight) for 18 months did not result in a significant difference in cognitive functions (ADAS-Cog), activities of daily living, or behavioral changes compared to placebo (van Gool et al., 2001). Analyses of covariance did not identify any specific subgroup defined by sex, age, ApoE genotype, study center, education, or baseline degree of deterioration, in which patients had benefited from the treatment.

An older pilot tolerability study of 20 probable Alzheimer's patients also reported that hydroxychloroquine treatment (200 mg, twice daily) for 11 weeks or hydroxychloroquine plus colchicine

(0.6 mg twice daily) for 12 weeks did not cause adverse effects on cognitive or behavioral assessment scores (Aisen et al., 2001).

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Hydroxychloroquine is absorbed and rapidly distributed to different tissues following oral administration and is able to cross the blood-brain barrier achieving concentrations 10-20 times greater than plasma concentrations (Mascolo et al., 2019). The terminal half-life is about 40 days, though a small amount of the drug can be found in the plasma, urine, and red blood cells several years after treatment (Tett et al., 1989).

Hydroxychloroquine may affect the central nervous system in many ways and precise mechanisms for different disease indications are not clearly delineated. Some mechanisms include the inhibition of immune response through an antagonistic effect on Toll-like receptors, inhibition of antigen presentation and lysosomal acidification, and improvements in cardiovascular functions by decreasing cholesterol levels (Mascolo et al., 2019).

It is also worth noting the mechanisms relevant for neuropsychiatric adverse events. Hydroxychloroquine can induce neuropsychiatric events, such as mood disorders and psychotic symptoms (Mascolo et al., 2019). Based on the European Medicine Agency, the most reported adverse reaction was depression, followed by insomnia, completed suicide, sleep disorder, and anxiety. According to the Important Medical Event list published by the European Medicine Agency, a total of 147 (22.6%) out of 647 reported reactions were serious. Different biological mechanisms have been hypothesized to underlie these effects, including cholinergic imbalance related to the inhibition of the acetylcholinesterase, prostaglandin E antagonism, the accumulation of toxic metabolites of hydroxychloroquine in the lysosome, and the down-regulation of glycoprotein-P in the blood–brain barrier. Hydroxychloroquine may also inhibit the serotonin transporter protein increasing serotonin levels in the synapse.

APOE4 interactions: Unknown.

Aging and related health concerns: Hydroxychloroquine treatment decreases the risk of cardiovascular disease and metabolic dysfunctions in patients with rheumatic diseases. Addition of hydroxychloroquine may also increase response rate and survival in some late-stage cancer patients.

Types of evidence:

- 9 meta-analyses or systematic reviews
- 3 clinical trials
- 1 observational study
- Several laboratory studies

Rheumatoid arthritis: SIMILAR OR LOWER BENEFIT COMPARED TO OTHER MEDICATIONS
A systematic review of 8 randomized controlled trials and 3 cohort studies in rheumatoid arthritis patients reported that hydroxychloroquine treatment (200-400 mg/day) showed clinical and structural efficacy similar to or lower than that for methotrexate (7.5-17.5 mg/week) or sulfasalazine (1.5-3 mg/day) in monotherapy (Rempenault et al., 2020).

Osteoarthritis: LACK OF BENEFIT
Two double-blind randomized controlled trials in hand osteoarthritis patients reported that hydroxychloroquine treatment (200 or 400 mg daily) failed to improve pain scores and other indices (Kingsbury et al., 2018; Lee et al., 2018).

Cardiovascular disease: DECREASED IN PEOPLE WITH RHEUMATIC DISEASES
Mortality is increased in patients with rheumatic disease as compared with the general population, and cardiovascular diseases are the main cause of the mortality.

In a large 2018 meta-analysis of 19 observational studies that included a total of 19,679 patients with rheumatic diseases (mostly systemic lupus erythematosus), hydroxychloroquine or chloroquine treatment was associated with a significantly reduced risk for cardiovascular disease (pooled RR=0.72; 95% CI, 0.56 to 0.94)(Liu et al., 2018). Results based on odds ratios showed a similar tendency towards a reduced risk of cardiovascular disease with chloroquine/hydroxychloroquine (pooled OR=0.41; 95% CI, 0.25 to 0.69). Chloroquine/hydroxychloroquine treatment was associated with a reduced risk of cardiovascular disease in patients with systemic lupus erythematosus (RR=0.64; 95% CI, 0.51 to 0.81), and a similar trend was seen in patients with rheumatoid arthritis (RR=0.81; 95% CI, 0.46 to 1.41) but without statistical significance.

A different 2018 meta-analysis of 9 studies in rheumatoid arthritis that examined the metabolic and cardiovascular effects of hydroxychloroquine reported that the mean differences between hydroxychloroquine users and non-users in levels of total cholesterol, LDL, HDL, and triglycerides were -9.8 mg/dL (95% CI, -14.0 to -5.6), -10.6 mg/dL (95% CI, -14.2 to -7.0), +4.1 mg/dL (95% CI, 2.2 to 6.0), and -19.2 mg/dL (95% CI, -27.2 to -11.1), respectively (Rempenault et al., 2018). A meta-analysis of 2 studies that evaluated lipid levels before and after 2 months or 3 months of hydroxychloroquine treatment showed that after initiation of hydroxychloroquine, the mean decreases in the levels of total cholesterol, LDL, and triglycerides were −13.1 mg/dL (−0.34 mmol/L; 95% CI, −20.9 to −5.3), −12.3 mg/dL (−0.32 mmol/L; 95% CI, −20.2 to −4.6), and −12.5 mg/dL (−0.14 mmol/L; 95% CI, −28.9 to 3.9), respectively, and the mean increase in HDL levels was +1.6 mg/dL (+0.04 mmol/L; 95% CI, −0.96 to 4.3).

The meta-analysis above included 3 studies comparing cardiovascular disease prevalence or incidence between hydroxychloroquine ever-users and never-users (Rempenault et al., 2018). In a retrospective study, the risk of cardiovascular morbidity was reduced among patients with rheumatoid arthritis who used hydroxychloroquine (OR=0.27; 95% CI, 0.16 to 0.46). In a case-control study, cardiovascular disease was also reduced with hydroxychloroquine treatment (adjusted OR=0.45; 95% CI, 0.10 to 2.0). In a retrospective study of rheumatoid arthritis patients, hydroxychloroquine use was associated with reduced incidence of cardiovascular disease (adjusted HR=0.60; 95% CI, 0.41 to 0.94) and the incidence of a composite of coronary artery disease, stroke, and transient ischemic attack (adjusted HR=0.67; 95% CI, 0.42 to 1.070).

In a mouse model of atherosclerosis and chronic kidney disease (ApoE knockout mice receiving high-fat diet), hydroxychloroquine treatment for 16 weeks significantly reduced the severity of atherosclerosis (Shukla et al., 2015). The treatment reduced the area of aortic atherosclerosis on en face examination by approximately 60% and resulted in a significant reduction in vascular endothelial dysfunction with improvement in vascular elasticity and flow patterns and better preservation of vascular wall thickness across multiple vascular beds. These beneficial effects were not due to any significant effect of hydroxychloroquine on inflammation, renal function, or lipid profile at the end of 16 weeks of therapy. Further studies are needed to define the exact mechanisms through which hydroxychloroquine confers these benefits in atherosclerosis.

Some biological mechanisms that are hypothesized include hydroxychloroquine's effects on lysosomes (Fox, 1993) which may result in an inhibition of cholesterol synthesis (Babary et al., 2018; Rempenault et al., 2018). Hydroxychloroquine also increases levels of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol (Ben-Zvi et al., 2012).

Hydroxychloroquine has also been shown to target endosomal NADPH oxidase, which is involved in many inflammatory and prothrombotic signaling pathways.

Diabetes and metabolic disease: IMPROVEMENT IN INSULIN, GLUCOSE, AND HbA1c
In a systematic review of 6 randomized controlled trials and 4 cohort studies (total of 55,776 subjects), hydroxychloroquine treatment (200 or 400 mg/day) showed significant improvement in insulin levels and substantial reduction in HbA1c, fasting plasma glucose, and postprandial blood glucose levels (Wondafrash et al., 2020). Reduction in lysosomal degradation of the internal insulin-insulin receptor complex and enhancement in insulin sensitivity and adiponectin levels are some of the hypothesized mechanisms for the antidiabetic effect of hydroxychloroquine.

In a double-blind randomized controlled trial of 267 patients with uncontrolled type 2 diabetes, hydroxychloroquine treatment (400 mg/day) for 24 weeks resulted in a 0.87% reduction in HbA1c, a 0.79 mmol/L reduction in fasting blood glucose, and a 1.77 mmol/L reduction in postprandial blood glucose levels (Pareek et al., 2014). A decrease in total cholesterol by 0.37 mmol/L and LDL by 0.23 mmol/L was also observed.

A meta-analysis of 3 studies in rheumatoid arthritis that examined the metabolic and cardiovascular effects of hydroxychloroquine reported that diabetes incidence was lower for hydroxychloroquine ever-users than never-users (HR=0.59; 95% CI, 0.49 to 0.70)(Rempenault et al., 2018). Based on a single study, change in HbA1c level from baseline to 3 months was −0.19±0.13% in hydroxychloroquine users versus −0.08±0.03% in methotrexate users.

The biological mechanisms of action for hydroxychloroquine effects on metabolism could be related to its effects on lysosomes that may reduce insulin degradation and inhibit cholesterol synthesis (Rempenault et al., 2018). *In vitro* and animal studies indicated that hydroxychloroquine improves insulin secretion and peripheral insulin sensitivity.

Cutaneous lupus erythematosus: IMPROVEMENT IN SYMPTOMS.
Cutaneous lupus erythematosus is an autoimmune disease affecting the skin. In a systematic review of 12 studies (5 retrospective, 3 prospective, 2 case series, and 2 randomized controlled trials) in cutaneous lupus erythematosus patients, hydroxychloroquine treatment (up to 400 mg/day) was shown to be effective in most (50-97%) of the patients (Shipman et al., 2020). One incidence of retinopathy, after a very high cumulative dose, was reported across all 12 studies that included a total of 852 patients.

Systemic lupus erythematosus: DECREASED RISK FOR CORONARY ARTERY DISEASE
Systemic lupus erythematosus is an autoimmune disorder that leads to inflammation and tissue damage involving multiple organ systems, such as skin, bone, heart, brain, kidney, and liver. It is a chronic inflammatory disease that is poorly understood, but involves hormonal, genetic, and environmental factors. Joint pain and fatigue are the most common initial findings, and with more advanced disease, renal, pulmonary, cardiovascular, and central nervous systems are affected. Patients with systemic lupus erythematosus have an elevated risk for coronary artery disease and cardiovascular events (Yang et al., 2019).

In a meta-analysis of 9 observational studies including a total of 823 patients with systemic lupus erythematosus, hydroxychloroquine use reduced mean LDL levels by 24.397 mg/dL (95% CI, 8.921-39.872)(Babary et al., 2018). Hydroxychloroquine reduced mean total cholesterol by 26.851 mg/dL (95% CI, 8.385–45.317).

In a retrospective cohort study of 826 patients with systemic lupus erythematosus, a significantly decreased hazard ratio (HR) for coronary artery disease was found in patients taking hydroxychloroquine for at least 318 days (HR=0.31; 95% CI, 0.12 to 0.76), after adjusting for chronic comorbidity (Yang et al., 2019). A low hazard ratio for coronary artery disease was observed in patients with a high cumulative dose of at least 100,267 mg hydroxychloroquine (HR=0.25; 95% CI, 0.09 to 0.66). However, there was no significant lowering of the risk for stroke.

In the pathogenic inflammation of systemic lupus erythematosus, production of different circulating autoantibodies induces immune complex deposition in different tissues and organs, leading to tissue destruction. Thrombosis-related antiphospholipid autoantibodies include anti-cardiolipin antibodies and anti-beta-2-GPI antibodies. In a mouse model of antiphospholipid syndrome, hydroxychloroquine reverses the prothrombotic state by reducing inflammation and preventing endothelial dysfunction (Miranda et al., 2019). *In vivo*, hydroxychloroquine can protect from inflammation and prothrombotic signaling pathways by inhibiting endosomal NADPH oxidase (Muller-Calleja et al., 2017). Protection from atherosclerosis may be associated with hydroxychloroquine's inhibition of toll-like receptor signaling, proinflammatory cytokine production, T-cell and monocyte activation, oxidative stress, and endothelial dysfunction (Floris et al., 2018).

Sjögren's syndrome: PAIN IMPROVED; NO BENEFIT FOR DRY EYES, DRY MOUTH, OR FATIGUE.
Sjögren's syndrome is a chronic autoimmune disease characterized by a wide spectrum of clinical manifestations, including lymphocytic infiltration and destruction of salivary and lacrimal glands, leading

to reduced lacrimal and salivary flow, dry eyes, dry mouth, and fatigue. Sjögren's syndrome also affects various organs including the skin, heart, lungs, kidney, gastrointestinal and endocrine systems, as well as the central and peripheral nervous systems. In a meta-analysis of 4 clinical trials in 215 patients with Sjögren's syndrome, hydroxychloroquine treatment did not show efficacy for relieving dry mouth and dry eyes when compared to placebo treatment (Wang et al., 2017). For fatigue, the effectiveness of hydroxychloroquine was lower than placebo. However, the efficacy of hydroxychloroquine in treating pain was superior to that of placebo.

Cancer: IMPROVEMENT WITH ADDITION OF HYDROXYCHLOROQUINE/CHLOROQUINE
The use of autophagy inhibitors is an emerging area in cancer treatment. A meta-analysis was performed to evaluate the clinical value of autophagy inhibitor-based therapy in cancer (Xu et al., 2018). A total of 293 patients were assessed across 7 clinical trials; 2 in glioblastoma, 1 in brain metastases or non-small cell lung cancer or breast cancer, 1 in pancreatic adenocarcinoma, 1 in non-Hodgkin lymphoma, 1 in metastatic pancreatic adenocarcinoma, and 1 in pancreatic cancer. Autophagy inhibitor-based therapy (e.g., hydroxychloroquine/chloroquine with gemcitabine, doxorubicin, radiation, etc.) showed higher overall response rate (RR=1.33; 95% CI, 0.95 to 1.86), progression-free survival (RR=1.72; 95% CI, 1.05 to 2.82), and overall survival (RR=1.39; 95% CI, 1.11 to 1.75) than the therapies without inhibiting autophagy.

Longevity: CHLOROQUINE TREATMENT DECREASES LIFESPAN IN MICE
In a longevity study in mice, chloroquine treatment (13.2 µg/ml in drinking water) from 10 months of age to end of life reduced mean lifespan; mean lifespan was 20.72 months with chloroquine treatment compared to 22.50 months in the control group (Hochschild 1973).

Safety: Long-term high-dose treatment may result in serious irreversible damage, such as retinopathy and cardiac toxicity, including cardiac failure and death. Hydroxychloroquine use during pregnancy may increase the risk for spontaneous abortion.

Types of evidence:

- 5 meta-analyses or systematic reviews, mostly based on observational studies
- 5 clinical trials
- 2 observational studies
- 2 reviews

Retinal Toxicity: Due to the risk of retinal toxicity, most patients should not receive a daily dose over 5 mg/kg/day or 400 mg of hydroxychloroquine sulfate salt, whichever is lower (Drugs.com). Retinopathy occurs at ~4%, and early changes may be reversible, but if advanced, the condition may progress despite discontinuation of hydroxychloroquine (Drugs.com). Baseline and periodic screening for retinopathy is necessary for rheumatologic uses and in long-term therapy. The first manifestation of retinal damage is pre-maculopathy, a reversible adverse effect characterized by changes in visual field or on fundoscopic examination, with no associated vision loss (Abarientos et al., 2011). However, with continuing therapy, a zone of depigmentation is seen around the pigmented macula that is surrounded with an area of pigment, resulting in a characteristic bull's eye lesion. Chloroquine at 250 mg/day is more oculotoxic than hydroxychloroquine at 400 mg/day.

The American Academy of Ophthalmology outlined risk factors associated with retinopathy following therapeutic use of hydroxychloroquine and chloroquine, and recommendations for screening (Marmor et al., 2016). These drugs appear to have a cumulative effect, as treatment duration longer than 5 years, cumulative doses higher than 1,000 g for hydroxychloroquine (and 460 g for chloroquine), and a high daily dose, were all shown to increase the risk of retinopathy.

Cardiac Toxicity: While the incidence is below 1% based on postmarketing reports, cardiomyopathy, resulting in cardiac failure, sometimes fatal, has been reported (Drugs.com). QT interval prolongation, ventricular arrhythmia, and torsades de pointes have been reported; therefore, concurrent use of other medications which may prolong the QT interval is not recommended.

In a systematic review, 86 articles were identified, reporting individual cases or short series, providing information on 127 patients (65.4% female)(Chatre et al., 2018). Most patients had been treated for a long time (median 7 years, minimum 3 days, maximum 35 years) and with a high cumulative dose (median 1,235 g for hydroxychloroquine and 803 g for chloroquine). Conduction disorders were the main side effect reported, affecting 85% of patients. Other non-specific adverse cardiac events included ventricular hypertrophy (22%), hypokinesia (9.4%), heart failure (26.8%), pulmonary arterial hypertension (3.9%), and valvular dysfunction (7.1%). For 78 patients reported to have been withdrawn from treatment, some recovered normal heart function (44.9%), while for others, resulted in irreversible damage (12.9%) or death (30.8%). Long-term administration of chloroquine and hydroxychloroquine has been associated with cardiac events, including myocardial thickening, restrictive cardiomyopathy, conduction disorders, and heart failure. The authors noted that chloroquine- or hydroxychloroquine-related cardiac manifestations, even conduction disorders without repercussion, may be initial

manifestations of toxicity, and are potentially irreversible. Therefore, treatment withdrawal is required when cardiac manifestations occur.

Potential mechanisms underlying cardiac toxicities include an increase in lysosomal pH, leading to impairment of lysosomal protein degradation, accumulation of ineffective autophagosomes, and accumulation of phospholipids and glycogen with myocyte vacuolization (Chatre et al., 2018).

Other Adverse Reactions: Gastrointestinal upset (nausea, vomiting, and diarrhea) is a common adverse effect and dividing doses, taking with food, and gradual dose escalation may improve tolerability (Drugs.com). Other adverse reactions for hydroxychloroquine may include ataxia, dizziness, emotional disturbance, headache, irritability, seizure, sensorineural hearing loss, vertigo, dermatologic reactions (rash, erythema of skin, psoriasis, dermatitis, pruritus, urticaria), hepatic reactions (acute hepatic failure, hepatic insufficiency), myopathy, ophthalmic reactions (corneal changes, decreased visual acuity, macular edema, nystagmus disorder, optic disc disorder, retinal vascular disease, retinitis, etc.), tinnitus, and bronchospasm.

Alzheimer's patients: 24% EXPERIENCED ONE OR MORE ADVERSE EVENT
In a double-blind randomized controlled trial of 168 early Alzheimer's patients, hydroxychloroquine treatment (200 or 400 mg, dependent on body weight) for 18 months did not result in a change in frequency or nature of serious adverse events, though a higher percentage (24%) of people on hydroxychloroquine experienced 1 or more adverse event compared to the placebo group (18%)(van Gool et al., 2001). Causes of death in the placebo group were bladder carcinoma and suicide (n=1 each). In the hydroxychloroquine group, causes of death were malignant neuroleptic syndrome, pneumonia, myocardial infarction, brain stem infarction, and a traffic accident (n=1 for each). Other adverse events included visual complaints, headache, and nausea.

An older pilot tolerability study in 20 probable Alzheimer's patients reported that hydroxychloroquine treatment (200 mg, twice daily) for 11 weeks or hydroxychloroquine plus colchicine (0.6 mg twice daily) for 12 weeks did not cause adverse effects on cognitive or behavioral assessment scores (Aisen et al., 2001). There were no significant side effects in subjects receiving hydroxychloroquine alone, but 2 subjects receiving hydroxychloroquine and colchicine experienced diarrhea.

Arthritis patients: A FEW INCIDENCES OF SERIOUS ADVERSE EVENTS
In a double-blind randomized controlled trial, 248 patients with hand osteoarthritis were treated with hydroxychloroquine (200 to 400 mg/day) or placebo for 12 months, and 15 serious adverse events were

reported, of which 3 were defined as possibly related to the drug: prolonged QT interval with ventricular arrhythmias, erythema multiforme, and acute generalized erythematous pustulosis (Kingsbury et al., 2018).

In a different double-blind randomized controlled trial of 196 patients with hand osteoarthritis, hydroxychloroquine treatment (400 mg/day) for 24 weeks did not result in any serious adverse events (Lee et al., 2018). However, in the hydroxychloroquine group, 3 patients reported a severe allergic reaction. Fifteen patients withdrew from the study (5 in placebo, 10 in hydroxychloroquine group) due to adverse events including allergic reaction, rash, or other dermatologic reaction.

Cancer patients: HIGH DOSES CAN ACCERATE THE ONSET OF RETINAL TOXICITY
A small observational study of 7 patients with non-small cell lung cancer who received high-dose hydroxychloroquine (1,000 mg/day) with erlotinib for at least 6 months reported that 2 developed retinal toxicity, one at 11 months and the other at 17 months of exposure (Leung et al., 2015). Damage was identified by optical coherence tomography (OCT) imaging, multifocal electroretinogram testing, and visual field testing. Neither patient had symptomatic visual acuity loss. These cases show that high doses of hydroxychloroquine can initiate the development of retinal toxicity within 1-2 years. Although synergy with erlotinib is theoretically possible, erlotinib has not been previously associated with retinal toxicity. These results also suggest that sensitive retinal screening tests should be added to ongoing and future clinical trials involving high-dose hydroxychloroquine to improve safety monitoring and preservation of vision. As is typical with early toxicity, anatomic signs appeared before patients recognized any loss of vision. With normal doses, the detection of retinal toxicity in less than 5 years of exposure is extremely rare. Results from this study show that hydroxychloroquine at higher doses can accelerate the onset of recognizable maculopathy, even in the absence of risk factors such as renal disease, coincident use of other retinotoxic medications, or preexisting maculopathy.

Cutaneous lupus erythematosus patients: RARE INCIDENCE OF RETINOPATHY
In a systematic review of 12 studies (5 retrospective, 3 prospective, 2 case series, and 2 randomized controlled trials) in cutaneous lupus erythematosus patients, hydroxychloroquine treatment (up to 400 mg/day) resulted in one incidence of retinopathy after a very high cumulative dose out of a total of 852 patients (Shipman et al., 2020). However, retinopathy and other serious adverse effects tend to occur with long-term treatment and many of the studies included in this systematic review are limited by short follow-up time.

Sjögren's syndrome patients: GASTROINTESTINAL ADVERSE EVENTS MOST COMMON
A meta-analysis of 4 clinical trials with a total of 215 patients with Sjögren's syndrome reported that gastrointestinal adverse effects were the most common adverse effects associated with hydroxychloroquine (Wang et al., 2017). Among the 116 patients in the hydroxychloroquine group, there were 9 adverse effects and 2 serious adverse events. In one study, a patient demonstrated liver damage after receiving hydroxychloroquine. In another study, there were 2 (urinary lithiasis, breast cancer) serious adverse events in the hydroxychloroquine group and 3 (meningioma, lipothymia, Epstein-Barr virus and cytomegalovirus pneumonia) in the placebo group.

Type 2 diabetes patients: 2 DEATHS, 1 DUE TO MYOCARDIAL INFARCTION
In a double-blind randomized controlled trial of 267 patients with uncontrolled type 2 diabetes, hydroxychloroquine treatment (400 mg/day) for 24 weeks did not result in hypoglycemia and one patient experienced non-proliferative diabetic retinopathy that the authors deemed was not related to hydroxychloroquine (Pareek et al., 2014). Serious adverse event of death was reported in two patients from the hydroxychloroquine group: one was due to acute myocardial infarction and the other due to acute pulmonary edema. The authors suggested that neither of these deaths were related to the study drug and speculated that these events can be explained by the increased underlying cardiovascular risk in type 2 diabetes patients. Most other adverse events were of mild to moderate intensity and were either not related or possibly related to study drugs.

Case study of psychomotor agitation: A case study of an elderly-onset rheumatoid arthritis patient reported an onset of psychomotor agitation with marked physical and verbal violence 10 days after taking 4 mg/kg/day of hydroxychloroquine (Manzo et al., 2017). The disappearance of agitation following targeted pharmacologic intervention and hydroxychloroquine interruption, its re-onset after reintroduction of hydroxychloroquine, suggested a causal relationship between hydroxychloroquine and psychomotor agitation. There are several possible mechanisms hypothesized for the onset of hydroxychloroquine-induced psychosis: the induction of a cholinergic imbalance with acetylcholine reduction, possibly mediated by prostaglandin E and IL-1; the accumulation of metabolic and toxic wastes as a result of lysosome dysfunction, and the down-regulation of P-glycoprotein at the blood–brain barrier.

Hydroxychloroquine use in pregnancy: POTENTIAL INCREASE IN SPONTANEOUS ABORTIONS
A meta-analysis of 1 randomized controlled trial and 7 observational cohort studies including pregnant women taking hydroxychloroquine (200-400 mg/day) reported no significant increases in rates of major congenital (OR=1.13; 95% CI, 0.59 to 2.17), craniofacial (OR=0.62; 95% CI, 0.13 to 3.03), cardiovascular

(OR=1.06; 95% CI, 0.29 to 3.86), genitourinary (OR=1.38; 95% CI, 0.42 to 4.53), nervous system malformations (OR=1.81; 95% CI, 0.31 to 10.52), stillbirth (OR=0.69; 95% CI, 0.35 to 1.34), low birth weight (OR=0.69; 95% CI, 0.21 to 2.27) or prematurity (OR=1.75; 95% CI, 0.95 to 3.24) (Kaplan et al., 2016). The rate of spontaneous abortions, however, was found to be significantly increased in hydroxychloroquine-exposed pregnancies (OR=1.85; 95% CI, 1.10 to 3.13). This may be associated with the underlying disease activity (bias by indication) and needs further investigation.

A review of 12 clinical studies with a total of 588 children born to pregnant women treated with chloroquine or hydroxychloroquine reported no evidence of fetal ocular toxicity (Osadchy et al., 2011).

***Drug interactions**:* There are 59 major drug interactions and 268 moderate drug interactions with hydroxychloroquine (Drugs.com). Some examples of major drug interactions with hydroxychloroquine include citalopram, escitalopram, haloperidol, methadone, mifepristone, nilotinib, and quinidine, which when taken together with hydroxychloroquine can increase the risk of an irregular heart rhythm that may be serious and potentially life-threatening (Drugs.com). Clozapine should also not be taken with hydroxychloroquine as the combination may increase the risk of a rare but serious and potentially fatal disorder called agranulocytosis that affects white blood cells (Drugs.com).

Sources and dosing: Hydroxychloroquine is a prescription medication used for the treatment of rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and discoid lupus erythematosus (Mascolo et al., 2019). For rheumatoid arthritis and lupus erythematosus, the dose is 200 to 400 mg daily (Drugs.com). Hydroxychloroquine is also used for the prophylaxis of malaria at 400 mg once weekly dose, and for a treatment of uncomplicated non-severe malaria infection at a dose of 800 mg once, followed by 400 mg at 6, 24, and 48 hours after initial dose (Drugs.com). Hydroxychloroquine is used off-label for dermatomyositis, porphyria cutanea tarda, Sjögren's syndrome, sarcoidosis, and Q fever. Clinical trials for Alzheimer's and diabetes have tested doses of 200 or 400 mg per day (van Gool et al., 2001; Pareek et al., 2014).

Research underway: There are over 100 ongoing clinical trials testing hydroxychloroquine (ClinicalTrials.gov). Some of these are in COVID-19 patients. Other studies are testing hydroxychloroquine in patients with multiple sclerosis, type 1 diabetes mellitus, myelodysplastic syndromes, prostate cancer, liver cancer, ovarian cancer, pancreatic cancer, pancreatitis, retinitis pigmentosa, melanoma, and other diseases.

Search terms:

Pubmed, Google:

- + cognitive, + ApoE4, + meta-analysis, + Cochrane, + lifespan, + mortality, + longevity, + atherosclerosis, + cancer, +randomized clinical trial

Websites visited for hydroxychloroquine or chloroquine:

- Clinicaltrials.gov
- DrugAge (1)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma
- Pharmapro.com (0)