Bijlage -1-

Rapid review

Wat zijn de bijwerkingen van (hydroxy)chloroquine bij (kwetsbare) ouderen met een medische indicatie voor het gebruik van (hydroxy)chloroquine?

Opgesteld door het Kennisinstituut van de Federatie Medisch Specialisten
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Uitgangsvraag: Wat zijn de bijwerkingen van (hydroxy)chloroquine bij (kwetsbare) ouderen met een medische indicatie voor het gebruik van (hydroxy)chloroquine?

Inleiding

Middelen die gebruikt kunnen worden bij de behandeling van patiënten met een ernstige COVID-19 infectie, zijn chloroquine en hydroxychloroquine. Er zijn signalen uit de kliniek, dat bij gebruik van deze middelen regelmatig bijwerkingen optreden. Het is onduidelijk of bijwerkingen bij kwetsbare ouderen een ernstiger beloop kennen dan in de jongere populatie. Het is belangrijk, indien deze bijwerkingen frequent voorkomen, om dit mee te nemen in de besluitvorming bij voorschrijven van (hydroxy)chloroquine.

Search and select

A systematic review of the literature was performed to answer the following question: What are the adverse effects of chloroquine or hydroxychloroquine in elderly patients?

P: elderly patients having a medical indication for the use of (hydroxy)chloroquine
I: use of (hydroxy)chloroquine
C: no use (hydroxy)chloroquine
O: mortality, cardiac events (cardiomyopathy, cardiac arrhythmias, prolonged QT interval), Gastro-intestinal signs and symptoms (nausea, vomiting, diarrea, stomach pain), Psychologically events: delirium, psychosis, anxiety, agitation, hypoglycemia

<u>Relevant outcome measures</u>

Mortality was considered a critical outcome measure for decision making. Cardiac events, Gastro-intestinal signs and symptoms, and psychologically events were considered an important outcome measures for decision making.

<u>Search and select (Methods)</u>

The database Embase (via Embase.com) was searched with relevant search terms until 31-3-2020. The systematic literature search resulted in 2072 hits. Studies were selected based on the following criteria adverse effects, hydroxychloroquine, chloroquine, systematic review, randomized controlled trial, observational studies (cohort study, case-control study – in case for chloroquine only as no RCT were available). In total 40 studies were initially selected based on title and abstract screening. After reading the full text, 36 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 4 studies were included.

Results

Four studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Kingsbury (2018) reported the results from a randomized controlled trial in patients with hand osteoarthritis. A total of 248 patients (mean age 63 years, SD 9) were randomized to either hydroxychloroquine (200 to 400 mg according to body weight, n = 124) or placebo (n = 124) for 12 months. Adverse events were recorded at 1, 3, 6, 9, 12, and 13 months.

Schneider (2013) described a cohort study with a nested case-control design, using a general practice research database. The intervention group consisted of patients having a pre-travel consultation between Jan 2001 – October 2009 who received a prescription for chloroquine and/or proguanil. Controls also visited for pre-travel consultation, but did not receive an antimalarial prescription. Follow-up was 540 days. Incidence rates for anxiety or psychosis and depression were calculated. Schneider (2013) also performed a nested case-control study, comparing cases (patients using chloroquine and being diagnosed with a neuropsychiatric disorder during follow-up), with controls (a random sample for the above described study population, without a psychiatric disorder). Overall, subjects in this study by Schneider (2013) were in general healthy and young. Subjects with a history of psychiatric disease, cancer, alcoholism or cancer were excluded. Important study characteristics and results are summarized in the evidence tables.

Saviola (2012) reported the results from a randomized controlled pilot study, without blinding. Thirty-eight patients were included and randomized to either a daily dose of 400 mg of hydroxychloroquine for 1 month, followed by a maintenance dose of 200 mg daily for the next 11 months (n =14; mean age 60.0, SD 7.1), or 300 mg of clodronate in 250 cc. of physiological saline solution for 7 days, followed by a maintenance dose of 100 mg intramuscular for 14 days every 3 months (n = 24; mean age 63.5, SD 7.4). All patients were explicitly requested at each visit to report any side effect.

Van Gool (2001) described a double-blind, parallel-group, multicentre trial in which randomly 168 patients with early Alzheimer's disease were assigned to hydroxychloroquine (200 or 400 mg dependent on bodyweight), or placebo for 18 months.
Patients were recruited through four memory clinics in Amsterdam between December, 1996, and October, 1998. Patients were randomly assigned to either a single dose of placebo or to hydroxychloroquine (400 mg in patients weighing >65 kg, or 200 mg in those weighing <65 kg). The average age of the patients in the hydroxychloroquine group (n=83) was 70,4 years (SD:8,3), with 46% (38) males. In the placebo group (n=85), the average age was 70,7 years, (SD: 8,5).
Important activities of daily living, cognitive functioning, and the presence of behavioural problems were assessed at baseline and after 9 and 18 months by research nurses. Checks were completed at intervals of 6 weeks by telephone or during a visit to the outpatient department, whichever the patient and caregiver preferred.

Results

Mortality - HCQ

Van Gool (2001) reported death in 6% (n=5) of the hydroxychloroquine population compared to 2% (n=2) in the placebo group (RR 2.56; 95% CI 0.51 to 12.83). Causes of death in the placebo group were bladder carcinoma and suicide, and in the hydroxychloroquine group causes of death were malignant neuroleptic syndrome, pneumonia, myocardial infarction, brain stem infarction, and a traffic accident.

Mortality – CQ
No studies reported mortality as side effect for chloroquine in elderly.

Cardiac events - HCQ
Kingsbury (2018) reported one case of prolonged QT interval with ventricular arrhythmias in the group treated with hydroxychloroquine, and no other cardiac events.

Cardiac events - CQ
No studies reported cardiac events as side effect for chloroquine in elderly.

Gastro-intestinal signs and symptoms - HCQ
Van Gool (2001) reported nausea in 2% (n=2) of the hydroxychloroquine population compared to 2% (n=2) in the placebo group.

Gastro-intestinal signs and symptoms - CQ
No studies reported gastro-intestinal signs and symptoms as side effect for chloroquine in elderly.

Psychological events - HCQ
No study reported psychological events as an adverse event for hydroxycholorquine.

Psychological events - CQ
Anxiety or stress-related disorders or psychosis: in the study by Schneider (2013) the overall incidence rate per 1000 person-years, in univariate analysis, was not elevated for individuals using chloroquine (10.6 (95% CI 8.0 to 14.1)), compared to unexposed individuals (9.8 (95% CI 9.0 to 10.6). Only in patients aged over 70 years, the incidence rates were different, 33.8 (95% CI 14.5 to 76.6) and 5.7 (95% CI 3.2 to 10.1), respectively. It might seem that this age group experiences these disorders more often, however, numbers were very small. For others age groups no differences in incidence of anxiety, stress-related disorders or psychosis were found. In the nested case-control study the odds-ratio for chloroquine/proguanil compared to no medication was 1.04 (95% CI 0.74 to 1.46) and therefore not clinically relevant, nor significant.

Depression: Schneider (2013) did not find any differences in incidence rates for depression. These were 7.7 (95% CI 5.5 to 10.7) for chloroquine/proguanil and 7.7 (95% CI 7.0 to 8.5) for unexposed individuals, respectively. In the nested case-control study the odds-ratio for chloroquine/proguanil compared to no medication was not significant, 1.07 (95% CI 0.71 to 1.59).

Hypoglycemia – HCQ/CQ
No study reported hypoglycaemia as an adverse event for hydroxychloroquine or chloroquine.

Saviola (2012) reported no adverse events in either study arm.

<u>Level of evidence of the literature</u>

Mortality - HCQ
Starting with a high level of evidence for randomized controlled trials, the level of evidence regarding the outcome measure mortality was downgraded by 2 levels to low because the small number of included patients (imprecision).

Mortality – CQ
There was no evidence regarding mortality

Cardiac events - HCQ
Starting at a high level of evidence for randomized controlled trials, the level of evidence regarding cardiac events was downgraded by 2 levels to low because of small number of included patients (imprecision).

Cardiac events - CQ
There was no evidence regarding cardiac events.

gastro-intestinal signs and symptoms - HCQ
Starting with a high level of evidence for randomized controlled trials, the level of evidence regarding the outcome measure gastro-intestinal signs and symptoms was downgraded by 2 levels to low because of the small number of included patients (imprecision).

gastro-intestinal signs and symptoms - CQ
There was no evidence regarding gastro-intestinal signs and symptoms.

Psychological events - HCQ
No evidence

Psychological events - CQ
Starting with a low level of evidence for observational studies, the level of evidence regarding both outcome measures, Psychological events (psychosis and depression), was downgraded by 1 level to very low because of small number of included patients (imprecision).

Hypoglycemia – HCQ/CQ
There was no evidence regarding hypoglycemia.

Conclusions

Low GRADE	*Mortality - HCQ* Hydroxychloroquine treatment may result in a slight increase in mortality in elderly patients treated with hydroxychloroquine, compared to elderly patients not treated with hydroxychloroquine. *Reference: van Gool (2001)*
No GRADE	*Mortality - CQ* No evidence *Reference: -*

Low GRADE	*Cardiac events - HCQ* Hydroxychloroquine treatment may result in a in a slight increase in the risk of cardiac events is increased in elderly patients treated with hydroxychloroquine, compared to elderly patients not treated with hydroxychloroquine. *Reference: Kingsbury (2018)*
No GRADE	*Cardiac events – CQ* No Evidence *Reference: -*

Low GRADE	*Gastro-intestinal signs and symptoms - HCQ* Hydroxychloroquine treatment may result in no difference in the risk of gastro-intestinal signs and symptoms is increased in elderly patients treated with hydroxychloroquine, compared to elderly patients not treated with hydroxychloroquine. *Reference: van Gool (2001)*
No GRADE	*Gastro-intestinal signs and symptoms – CQ* No evidence *Reference: -*

No GRADE	*Psychological events - HCQ* No evidence *Reference: -*
Very Low GRADE	*Psychological events – CQ* We are unsure whether the risk of psychological events (psychosis or depression) is increased in patients using chloroquine, compared to patients not using this medication *Reference: Schneider 2013*

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No GRADE	*Hypoglycemia - HCQ* No evidence *Reference: -*
No GRADE	*Hypoglycemia - CQ* No evidence *Reference: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er zijn zeer weinig studies vergelijkende studies beschikbaar die bijwerkingen vergeleken tussen populaties ouderen met en zonder behandeling met (hydroxy)chloroquine.
Op basis van literatuuronderzoek is enkel lage kwaliteit bewijs gevonden. Er kunnen geen duidelijke conclusies worden getrokken over het voorkomen van bijwerkingen bij gebruik van chloroquine en hydroxychloroquine bij oudere patiënten.

Het Lareb registreert gemelde bijwerkingen van chloroquine en hydroxychloroquine. Op deze website word en het aantal meldingen weergegeven voor chloroquine onderverdeeld naar leeftijd. Van de 77 meldingen was 16,9% van de meldingen afkomstig van mensen boven de 60 jaar. Voor hydroxychloroquine worden 34% van de meldingen (n=536) gedaan door patiënten boven de 60 jaar. Bijwerkingen betreffen o.a: Klachten aan: ademhalingsstelsel en borstkas (18), Bloed- en lymfestelsel (9), Bloedvaten (13), Huid- en onderhuid (191), maag-darmstelsel (137), Toedieningsplaats en lichaam algemeen (171), Psychisch (44), Oor en evenwichtsorgaan (30).

Literatuur

Kingsbury, S. R. and Tharmanathan, P. and Keding, A. and Ronaldson, S. J. and Grainger, A. and Wakefield, R. J. and Arundel, C. and Birrell, F. and Doherty, M. and Vincent, T. and Watt, F. E. and Dziedzic, K. and O'Neill, T. W. and Arden, N. K. and Scott, D. L. and Dickson, J. and Garrood, T. and Green, M. and Menon, A. and Sheeran, T. and Torgerson, D. and Conaghan, P. G (2018). Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis a randomized trial, Annals of Internal Medicine – 168 (6) , pp. 385-395

Saviola, G. and Abdi-Ali, L. and Campostrini, L. and Sacco, S. and Baiardi, P. and Manfredi, M. and Mannoni, A. and Benucci, M (2012). Clodronate and hydroxychloroquine in erosive osteoarthritis: a 24-month open randomized pilot study. Mod Rheumatol, 22 (2), pp. 256-63

Schneider, C., Adamcova, M., Jick, S. S., Schlagenhauf, P., Miller, M. K., Rhein, H. G., & Meier, C. R. (2013). Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. Travel medicine and infectious disease, 11(2), 71-80.

Van Gool, W. A. and Weinstein, H. C. and Scheltens, P. and Walstra, G. J. (2001). Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study, Lancet 358 (9080), pp. 455-60

Bijwerkingencentrum Lareb. (2020, 1 april). Chloroquine. Geraadpleegd van https://www.lareb.nl/nl/databank/Result?formGroup=&atc=P01BA01&drug=CHLOROQUINE

Evidence table for intervention studies

Research question: Do patients using chloroquine or hydroxychloroquine have an increased risk for psychiatric disorders or psychological complaints?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Van Gool, 2001	Type of study: RCT - double-blind, parallel-group, multicentre trial Setting and country: Netherlands Funding and conflicts of interest: The work was supported by Praeventiefonds (grant 28-2710) and Stichting Polikliniek voor Geheugenstoornissen AMC. Sanofi Winthrop provided hydroxychloroquine and placebo tablets.	Inclusion criteria: Individuals were eligible if they fulfilled criteria for a diagnosis of probable Alzheimer's disease, as outlined by the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders. Exclusion criteria: patients with early signs of maculopathy N total at baseline: N - total=168 N - intervention: 83 N – placebo: 85 Important prognostic factors[2]: *Age:* *I: 70.4 (8.3)* *C: 70.7 (8.5)* *Sex: (% male)*	Describe intervention (treatment/procedure/test): A single dose of hydroxychloroquine (400 mg in patients weighing >65 kg, or 200 mg in those weighing <65 kg). Important activities of daily living, cognitive functioning, and the presence of behavioural problems were assessed at baseline and after 9 and 18 months by one of two research nurses, who were otherwise not involved in the clinical care of patients. We did checks at intervals of 6 weeks by telephone or during a visit to the outpatient department, whichever the patient and caregiver preferred. These checks allowed us to monitor compliance, concurrent medications, and side effects, and to address any other concerns.	Describe control (treatment/procedure/test): A single dose of placebo Procedure – see intervention	Length of follow-up: 18 months Loss-to-follow-up: N/A N=6 hydroxychloroquine group N=7 in placebo group Incomplete outcome data: N/A	Outcome measures and effect size (include 95%CI and p-value if available): The proportions of patients with adverse events in the hydroxychloroquine group did not differ significantly from those in the placebo group. Death: n=5 (6%) vs 2 (2%) Nausea: n=2 (2%) vs 2 (2%)	Aim: We aimed to establish the effect of the anti-inflammatory drug hydroxychloroquine on the progression of dementia. Author's conclusion: Anti-inflammatory treatment with hydroxychloroquine for 18 months does not slow the rate of decline in minimal or mild Alzheimer's disease. No differences in adverse events between intervention and control population.

		I: 46% *C: 39%* Groups comparable at baseline? yes					
Saviola, 2012	Type of study: RCT, open label Setting and country: Hospital based, Italy Funding and conflict of interest: None reported	<u>Inclusion criteria:</u> Patients with erosive osteoarthritis between 45 and 75 years; diagnosed according to radiographic criteria; visual analogue scale (VAS) pain rating >4/10; ≥2 proximal interphalangeal joints or distal interphalangeal joints involved; treatment with glucocorticoids, disease-modifying anti-rheumatic drug (DMARDs), or SYSADOAs stopped at least 3 months prior the start of the study <u>Exclusion criteria:</u> inactive erosive osteoarthritis; erosive osteoarthritis with functionally	Describe intervention (treatment/procedure/test): Hydroxychloroquine, daily dose of 400 mg for 1 month, followed by a maintenance dose of 200 mg daily for the next 11 months All patients were explicitly requested at each visit to report any side effect. No biohumoural side effects emerged from monitoring hemocrome, glycemia, alkaline phosphatase, transaminase, creatininemia, calcemia, and urine.	Describe control (treatment/procedure/test): 300 mg of clodronate in 250 cc. of physiological saline solution for 7 days, followed by a maintenance dose of 100 mg i.m. for 14 days every 3 months.	<u>Length of follow-up</u>: All patients were to be evaluated at baseline and at months 3, 6, 12, 18, and 24 after the onset of the treatment. HCQ follow-up was stopped at 12 months because of inefficacy related to the primary outcome pain reduction <u>Loss-to-follow-up:</u> HCQ: 8 out of 14 CLO: <u>1 out of 24</u> <u>Incomplete outcome data:</u> N/A	Outcome measures and effect size (include 95%CI and p-value if available): None of the 38 enrolled patients reported serious side effects.	Aim: To compare the efficacy of CLO and HCQ for treating erosive osteoarthritis of the hand. Author's conclusions: There was no difference in adverse events between the groups.

		irreversible damages (ankylosis); renal, cardiovascular, neurologic, psychiatric, neoplastic, retinal, or rheumatic diseases other than erosive osteoarthritis. <u>N total at baseline:</u> N total = 38 N HCQ = 14 N CLO = 24 <u>Important prognostic factors:</u> Age: HCQ: 60.0 (7.1) CLO: 63.5 (7.4) Sex: (% male) HCQ: 7 % CLO: 4 % <u>Groups comparable at baseline?</u> yes					
Kingsbury, 2018	Type of study: RCT, double-blind Setting and country: 13 primary and secondary care centers in England. Funding and conflict of interest: Arthritis Research UK grant. SK and PC: partially	<u>Inclusion criteria</u>: age ≥ 18 years ; reported inadequate response or adverse effects with existing medication; had moderately severe symptoms for more than half of days in the past 3 months;	Describe intervention (treatment/procedure/test): Hydroxychloroquine (200 to 400 mg based on body weight) for 12 months Computer-generated 1:1 randomisation	Describe control (treatment/procedure/test): Placebo visually identical to intervention drug for 12 months Computer-generated 1:1 randomisation	<u>Length of follow-up:</u> Adverse events data collection after 1 3, 6, 9, 12, and 13 months. <u>Loss-to-follow-up: 16</u> Intervention: 11 Control: 5 <u>Incomplete outcome data:</u> N/A	Outcome measures and effect size (include 95% CI and p-value if available): <u>Serious adverse events in the intervention group:</u> 7 in 7 patients (5.6 % of randomised patients). Related to investigational medical product: 3 (prolonged QT interval with ventricular arrhythmias,	Aim: To determine the effectiveness of hydroxychloroquine versus placebo as an analgesic treatment of hand osteoarthritis Author's conclusions: No conclusion about adverse events reported in the article

	funded by the NIHR through the Leeds Biomedical Research Centre. MD: partially funded by a Knowledge Mobilisation Research Fellowship from the NIHR. AK: grants from Arthritis Research UK. AG: personal fees from GE Healthcare and Levicept. Director of LivingCare Imaging. FB: grants from Arthritis Research UK and the NIHR. MD grants from AstraZeneca, personal fees from AstraZeneca, Nordic Bioscience, Grünenthal, and Roche. FW: grants from Astellas and Pfizer. KD: grants from Arthritis Research UK Primary Care Centre, the NIHR, Knowledge Mobilisation Research Fellowship and EIT Health, nonfinancial support from National Institute of Health and Care Excellence (NICE), member of the NICE Quality Standards Group for	osteoarthritis (American College of Rheumatology criteria); radiographs (past 5 years) consistent with osteoarthritis; stable/no change to/no use of analgesics for at least 4 weeks or glucosamine or chondroitin for at least 4 months; informed consent. <u>Exclusion criteria</u>: inflammatory arthritis; psoriasis; involvement of only the carpometacarpal joint (CMCJ) or predominant CMCJ pain; use of oral, intramuscular, intra-articular, or intravenous steroids, other antisynovial agents, or any new hand osteoarthritis therapies during the past 2 months; intra-articular hyaluronans in the past 6 months; uncontrolled disease states in				erythema multiforme, and acute generalized erythematous pustulosis) Serious adverse events in the control group: 8 in 8 patients (6.5 % of randomised patients) <u>Non-serious adverse events</u> in intervention group: 152 in 61 patients (49.2 % of randomised patients) Non-serious adverse events in control group: 135 in 53 patients (42.7 % of randomised patients) The difference between intervention and control was not statistically tested.	

	Osteoarthritis, member of the NICE Osteoarthritis Guidelines Development Group CG 59 (2008) and CG 117 (2014), invited speaker at the Bone and Joint Decade 2015 Conference (Oslo), invited speaker for osteoarthritis Research Society International. TO: grants from Arthritis Research UK. NA: grants from BIOIBERICA and Novartis, perrsonal fees from Bioventus; the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; Flexion; Freshfields Bruckhaus Deringer; Merck; Regeneron; and Smith & Nephew . DS: grants from Arthritis Research UK. DT: grants from Arthritis Research UK. PC: personal fees from AbbVie, Flexion, Novartis, Pfizer, Samumed, and TissueGene.	which flares are commonly treated with corticosteroids; serious uncontrolled medical conditions; unexplained vision impairment; pregnancy or lactation; melanoma or nonskin cancer in the past 3 years; significant hematologic or biochemical abnormalities. <u>N total at baseline</u>: 248 Intervention: Hydroxychloroquine Control: placebo N HCQ = 124 N placebo = 124 <u>Important prognostic factors</u>[2]: *age ± SD:* *I: 62.8 ± 9.1* *C: 62.5 ± 9.2* *Sex: (% male)* *HCQ: 22 %* *placebo: 15 %* Groups comparable					

		at baseline? yes					

Notes: IR = incidence rate; RA = rheumatoid arthritis; HCQ = hydroxychloroquine; CLO = clodronate

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Evidence table observational studies

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Schneider 2013	Type of study: 1. cohort study with 2. a nested case control study Setting and country: General Practice Research Database (GPRD), UK Funding and conflicts of interest: MA and HR are employees of F. Hoffmann-La Roche. MM is an employee of Genentech Inc. PS received speakers' honoraria/research grants from GSK and speakers' honoraria, research grants and consultancy fees from Hoffmann-La	Inclusion criteria: Jan 1st '01- Oct 1st '09; pre-travel consultation within 1 week of prescription Exclusion criteria: diagnosis of malaria prior to start of anti-malarial drug use, patients with history of cancer, alcoholism, RA; outcome of interest prior to using anti-malarial drugs N total at baseline: Intervention: chloroquine/ proguanil Control: no	1. Describe intervention (treatment/procedure/test): ≥ 1 prescription of mefloquine, chloroquine and/or proguanil or atovaquone/proguanil; only subjects who used anti-malarial drugs for malaria prophylaxis were included 2. Describe cases: using chloroquine, diagnosed with incident neuropsychiatric disorder during follow-up	1. Describe control (treatment/procedure/test): patients not exposed to any antimalarial, who had a pre-travel consultation One non-user was matched to one user on age, sex, and general practice 2. Describe controls: random sample from study population, without psychiatric disorder, at random up to six controls per case	Length of follow-up: 1. until the person became a case, died, or 540 days post exposure, or computer record ended 2. within 540 days of index date (date of diagnosis). Loss-to-follow-up: N/A Incomplete outcome data: N/A	Outcome measures and effect size (include 95%CI and p-value if available): **1. incidence rates per 1000 person-years** IR anxiety or stress-related disorders or psychosis combined Chloroquine/proguanil: N=47; 10.6 (8.0-14.1) Age 70+; N=5; Unexposed: 33.8 (14.5-76.6) N=537; 9.8 (9.0-10.6) Age 70+: N=11; 5.7 (3.2-10.1) Depression: Chloroquine/proguanil: N=34; 7.7 (5.5-10.7) Unexposed: N=423; 7.7 (7.0-8.5) **2. adjusted odds ratio:** anxiety or stress-related disorders or psychosis combined Chloroquine/proguanil N exp 47; N unexp 537 OR 1.04 (95% CI 0.74-1.46)	Aim: risk assessment of developing first-time diagnosis of depression, anxiety, stress related disorders, psychosis, in patients using chloroquine and/or proguanil for malaria chemoprophylaxis, as compared to unexposed travelers. Author's conclusion: The risk of neuropsychiatric disorders was similar for users and for non-users of antimalarial chemoprophylaxis, with evidence for elevated risks in some subgroups

	Roche.	antimalarials N chloroquine = 47 N unexposed = 537 <u>Important prognostic factors</u>[2]: *age ± SD:* *I:* N/A *C:* N/A Groups comparable at baseline? yes				<u>Depression:</u> N exp=33; N unexp=423 1.07 (95% CI 0.71-1.59)	

Notes: IR = incidence rate; RA = rheumatoid arthritis

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Risk of bias table for intervention studies

Research question: Do elderly patients using chloroquine or hydroxychloroquine have an increased risk for adverse events?

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Van Gool 2001	Treatments assignment was done according to a computer generated code in a 1/1 ratio in randomised permuted blocks of four for treatment centres. Allocation codes were held at the Academic Medical Centre pharmacy that dispensed all trial medication.	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely
Saviola, 2012	Patients were initially randomized with a 1:1 ratio into two groups (A and B). – procedure not clearly described	unclear	likely	Likely	unclear	unlikely	likely	unclear
Kingsburry, 2018	Randomization (1:1) was computer-generated (with PRISYM ClinTrial [PRISYM ID]) in advance by the contract manufacturer using random permuted blocks without stratification. The contract manufacturer prepared the trial drug with over	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely

	encapsulation to create identical intervention and placebo-control products with no involvement from the research team and assigned intervention and control drug packs in sequence to recruiting sites.							

Risk of bias table observational studies

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Schneider 2013	unlikely	unlikely	unclear	likely

Table of excluded studies

Author and year	Reason for exclusion
Gupta, 2019	Does not fit PICO
Haas, 2019	Does not fit PICO
Krishnamurthi, 2019	Does not fit PICO
Kumar, 2019	Does not fit PICO
Malhotra, 2019	Does not fit PICO
McGill, 2019	Does not fit PICO
Raquel Benedita Terrabuio, 2019	Does not fit PICO
Majzoobi, 2018	Does not fit PICO
Liu, 2018	Does not fit PICO
Pavelka, 2017	Does not fit PICO
Sharma, 2016	Does not fit PICO
Valecha, 2016	Does not fit PICO
Gottenberg, 2014	Does not fit PICO
Mahalingam, 2014	Does not fit PICO
Pareek, 2014	Does not fit PICO
Teixeira, 2014	Does not fit PICO
Liu, 2013	Does not fit PICO
Saini, 2013	Does not fit PICO
Goldberg, 2012	Does not fit PICO
Singal, 2012	Does not fit PICO
Marko, 2011	Does not fit PICO
Santoshkumar, 2010	Does not fit PICO
Yeshiwondim, 2010	Does not fit PICO
Pareek, 2008	Does not fit PICO
Gubar, 2008	Only available in Russian
Tjitra, 2008	Does not fit PICO
Fong, 2007	Does not fit PICO
Aisen, 2001	Does not fit PICO, observational study, no control group
Stein, 2000	Does not fit PICO
Sokka, 1999	Does not fit PICO
Marshall, 1999	Paper not found
Hera study group, 1995	Does not fit PICO
Faarvang, 1993	Does not fit PICO
Haar, 1993	Does not fit PICO
Nuver-Zwart, 1989	Does not fit PICO
Hansen, 1976	Does not fit PICO