

Bijlage -1-

Rapid review

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

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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

15

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

20 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

25 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

30 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

35 <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.

40 Search and select (Methods)

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

- 45 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.
- 50 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

- 10 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
- 15 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.
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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

25 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

35 <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).</p>

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

40 were completed at intervals of 6 weeks by telephone or during a visit to the outpatient department, whichever the patient and caregiver preferred.

<u>Results</u>

Mortality - HCQ

45 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.

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Mortality – CQ

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

Cardiac events - HCQ

5 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.

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

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

Psychological events - HCQ

20 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
- 30 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.

- 35 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).
- 40 *Hypoglycemia HCQ/CQ* No study reported hypo

No study reported hypoglycaemia as an adverse event for hydroxychloroquine or chloroquine.

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

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Level of evidence of the literature

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

5 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

10 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.

20 *Psychological events - HCQ* No evidence

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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

30 There was no evidence regarding hypoglycemia.

Conclusions

Conclusions	
Low GRADE	<i>Mortality - HCQ</i> 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	<i>Mortality - CQ</i> No evidence <i>Reference: -</i>

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: -

	Gastro-intestinal signs and symptoms - HCQ
Low GRADE	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)
	Gastro-intestinal signs and symptoms – CQ
No GRADE	No evidence Reference: -

	Psychological events - HCQ
No GRADE	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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	Hypoglycemia - HCQ
No GRADE	No evidence Reference: -
	Hypoglycemia - CQ
No GRADE	No evidence <i>Reference:</i> -

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u> 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

5 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),
- 15 Psychisch (44), Oor en evenwichtsorgaan (30).

Literatuur

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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	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	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	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%Cl 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.
	Winthrop provided hydroxychloroquine and placebo tablets.	maculopathy <u>N total at baseline</u> : N - total=168 N - intervention: 83 N - placebo: 85 <u>Important</u> <u>prognostic factors²</u> : <i>Age:</i> <i>I: 70.4 (8.3)</i> <i>C: 70.7 (8.5)</i> <i>Sex: (% male)</i>	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.				

Saviola,	Type of study:	I: 46% C: 39% Groups comparable at baseline? yes	Describe intervention	Describe control	Length of follow-up:	Outcome measures and	Aim:
2012	RCT, open label Setting and country: Hospital based, Italy Funding and conflict of interest: None reported	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	(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.	(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.	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 Loss-to-follow-up: HCQ: 8 out of 14 CLO: <u>1 out of 24</u> Incomplete outcome data: N/A	effect size (include 95%Cl and p-value if available): None of the 38 enrolled patients reported serious side effects.	The 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.	
N total at baseline:	
N total = 38	
N HCQ = 14	
N CLQ = 24	
Important	
prognostic factors:	
Age:	
HCQ: 60.0 (7.1)	
CLO: 63.5 (7.4)	
Sex: (% male)	
HCQ: 7 %	
CLO: 4 %	
Groups comparable	
at baseline? yes	
Kingsbury, Type of study: Inclusion criteria: Describe intervention Describe control Length of follow-up: Outcome measurement	res and Aim: To determine the
2018 RCT, double-blind age \geq 18 years ; (treatment/procedure/test): (treatment/procedure/test): Adverse events data effect size (include the second secon	
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Research UK grant. days in the past 3 data: N/A (prolonged QT in	terval with the article
SK and PC: partially months; ventricular arrhy	thmias,

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Knowledge antisynovial	Care Centre, the	intravenous			
	NIHR,	steroids, other			
	Knowledge	antisynovial			
in the second seco	Mobilisation	agents, or any new			
Research Fellowship hand osteoarthritis	Research Fellowship	hand osteoarthritis			
and EIT Health, therapies	and EIT Health,	therapies			
nonfinancial support during the past 2					
from National months; intra-	from National	months; intra-			
Institute of Health articular	Institute of Health	articular			
and Care Excellence hyaluronans in hyaluronans in	and Care Excellence	hyaluronans in			
(NICE), member of the past 6 months;	(NICE), member of				
the NICE Quality uncontrolled	the NICE Quality	uncontrolled			
Standards Group for disease states in	Standards Group for	disease states in			

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

at baseline? yes

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

5

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	Inclusion criteria: Jan 1 st '01- Oct 1 st '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	 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 Describe cases: using chloroquine, diagnosed with incident neuropsychiatric disorder during follow-up 	 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 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%Cl and p-value if available):1. incidence rates per 1000 person-yearsIR anxiety or stress-related disorders or psychosis combinedChloroquine/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)	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
	Genentech Inc. PS received speakers' honoraria/research grants from GSK and speakers' honoraria, research grants and consultancy fees from Hoffmann-La	interest prior to using anti- malarial drugs <u>N total at</u> <u>baseline</u> : Intervention: chloroquine/ proguanil Control: no				Unexposed: N=423; 7.7 (7.0-8.5) 2. adjusted odds ratio: <u>anxiety or stress-related</u> <u>disorders or psychosis</u> <u>combined</u> Chloroquine/proguanil N exp 47; N unexp 537 OR 1.04 (95% Cl 0.74-1.46)	

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

Notes: IR = incidence rate; RA = rheumatoid arthritis

Risk of bias table for intervention studies

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

Study	Describe method of randomisation ¹	Bias due to inadequate concealment of	Bias due to inadequate	Bias due to inadequate	Bias due to inadequate	Bias due to selective	Bias due to loss to follow-up?⁵	Bias due to violation of
reference	randomisation	concealment of allocation? ²	blinding of participants to treatment	blinding of care providers to treatment	blinding of outcome assessors to treatment	outcome reporting on basis of the results? ⁴	tonow-up?	intention to treat analysis? ⁶
(first			allocation? ³	allocation? ³	allocation? ³			
author,								
publication		(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)
year) Van Gool	Treatments assignment	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely
2001	was done according to	uninkery	utilikely	uninkery	uninkery	uninkery	uninkery	uniikely
2001	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.							
Saviola,	Patients were initially	unclear	likely	Likely	unclear	unlikely	likely	unclear
2012	randomized with a 1:1	unciedi	likely	LIKEIY	unciedi	uninkery	likely	unciedi
2012	ratio into two groups (A							
	and B). – procedure not							
	clearly described							
Kingsburry,	Randomization (1:1)	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely	unlikely
2018	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							

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.				

5

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	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups? ²		Bias due to inadequate adjustment for all important prognostic factors? ⁴
	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(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