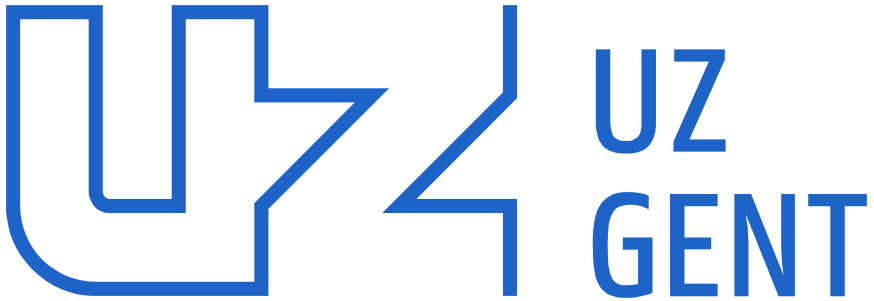

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Research

JAMA Neurology | Original Investigation

Efficacy of Benzodiazepines or Antihistamines for Patients With Acute Vertigo

A Systematic Review and Meta-analysis

Benton R. Hunter, MD; Alfred Z. Wang, MD; Antonino W. Bucca, MD; Paul I. Musey Jr, MD; Christian C. Strachan, MD; Steven K. Roumpf, MD; Steven L. Propst, MD; Alexander Croft, MD; Laura M. Menard, MIS; Jonathan M. Kirschner, MD

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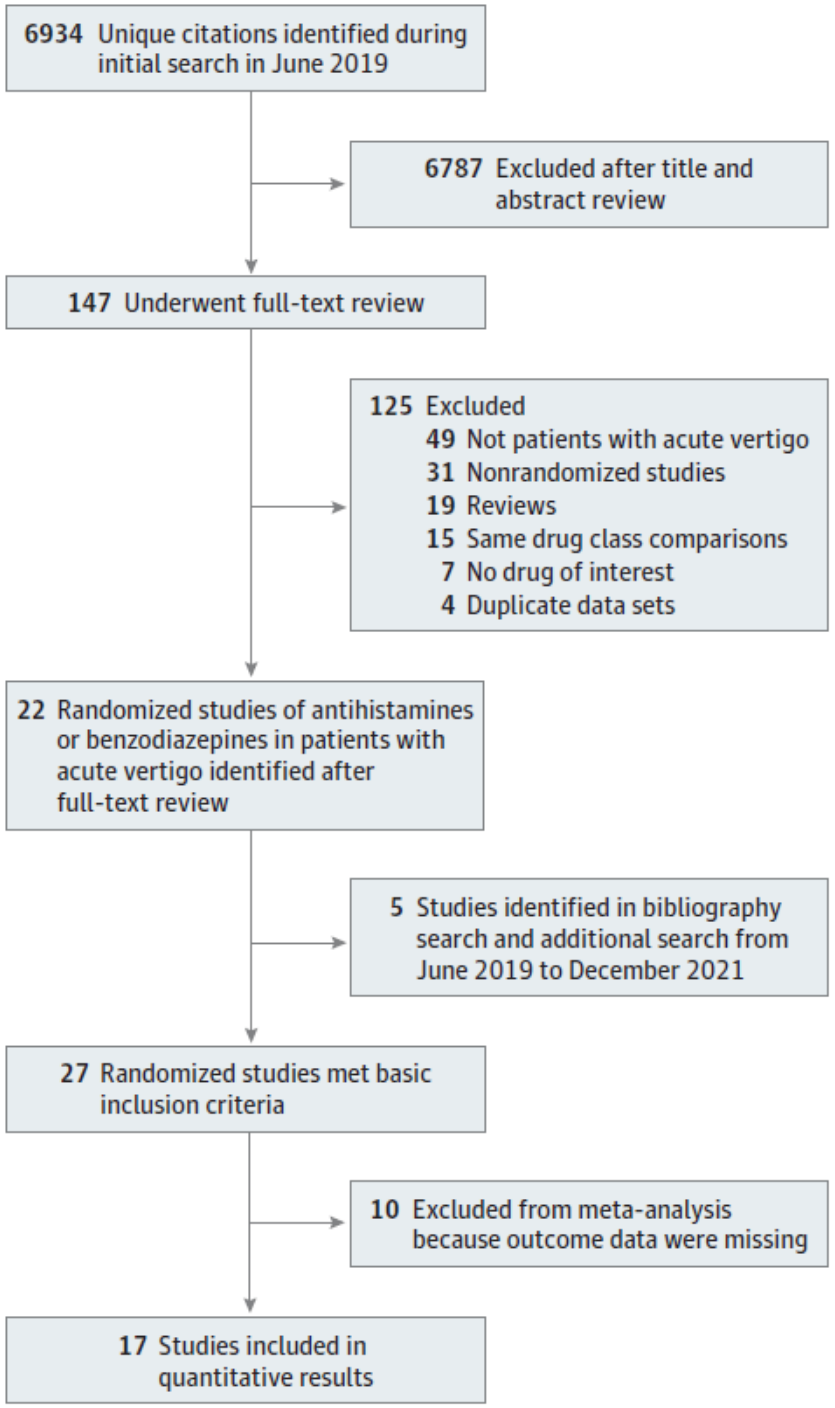

Studies :

Benzos of antihist : <u>vergeleken</u> met andere therapie of met placebo of met ‘geen interventie’

Acute vertigo voor 2 weken of minder

 HUNTER BR, ET AL.
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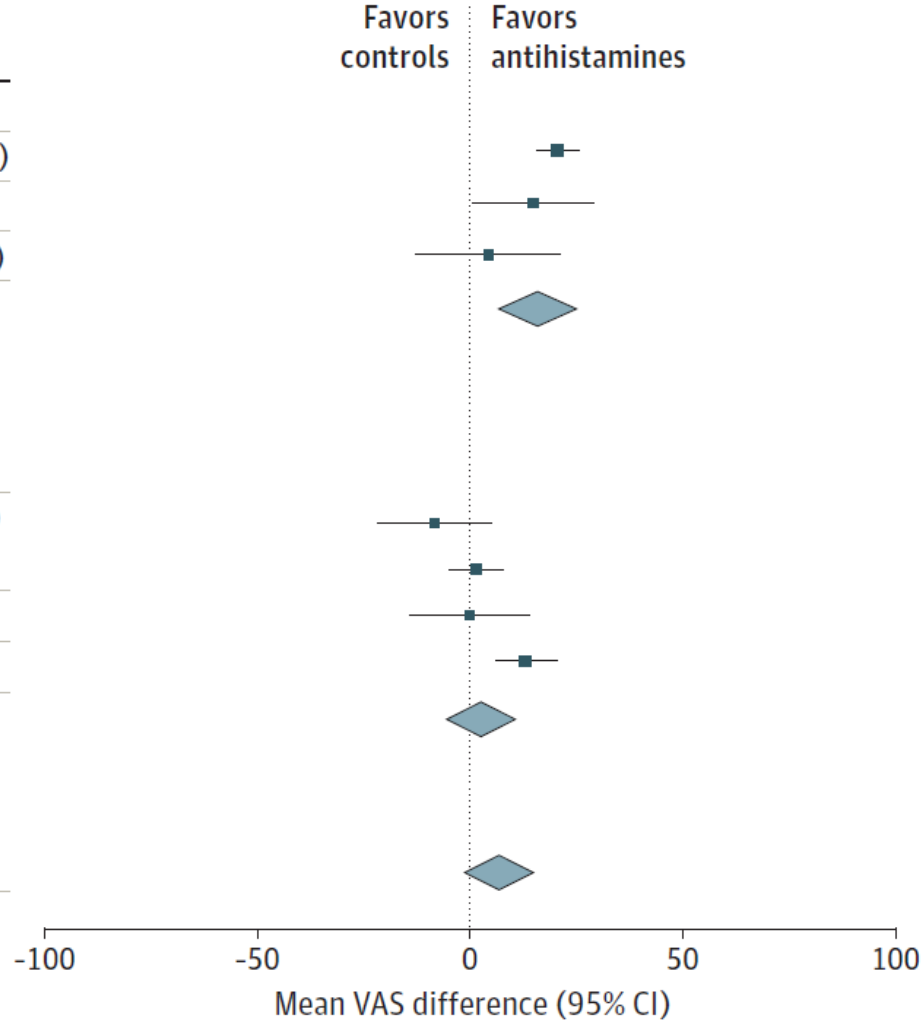
Table 2. Randomized Clinical Trials Included in the Systematic Review

Source	Country	Blind or open label	No. of patients	Vertigo type	Medications, controls, and comparators	Main outcomes reported	Inclusion criteria	Main exclusion criteria	Main results
Amini et al,[21] 2014	Iran	Double blind	184	Peripheral	Promethazine (25 mg) vs lorazepam (2 mg) (IV)	Change in 100-point vertigo VAS score; change in 100-point VAS score nausea at 2 h (reported as average with SD); need for repeat dosing	Patients in ED aged 18-65 y with signs and symptoms consistent with peripheral vertigo	Brain injury, central vertigo, pregnancy, contraindication to medications, prior treatment, or drug-induced or orthostatic dizziness	More improvement in both vertigo and nausea VAS scores with promethazine; less need for rescue doses with promethazine
Boniver et al,[22] 1978	Belgium	Double blind	18	Central (vascular)	Flunarizine taper from 40 to 10 mg/d vs placebo for 3 mo (orally)	Subjective report of resolved, improved, no change, or worse at 1 wk and 1, 2, and 3 mo; also nystagmometric data	"Definite vertigo" defined by otolaryngology examination, electronystagmography, and audiometric testing	None specified	Flunarizine better at 2 mo but not at 1 or 3 mo
Castellini et al,[23] 1969	Italy	Double blind	44	Mixed, including traumatic, Meniere disease, and central nervous system associated	Cinnarizine-containing gel tabs (15 mg) or suppositories (25 mg) vs placebo for 7-60 d	Resolved enough to be satisfactory to the patient or did not; time frame only given in tables; also nystagmometric data	Unselected vertiginous patients with varying final diagnoses, including Meniere disease, traumatic vertigo, and labyrinthitis	None specified	Cinnarizine better than placebo at improving vertigo
Doğan et al,[24] 2015	Turkey	Double blind	94	Peripheral, but not specified	Dimenhydrinate (100 mg) vs piracetam (2000 mg) (IV)	Change in 10-point VAS vertigo score at 30 min (still and ambulatory); need for rescue benzodiazepines	Adults in ED with vertigo defined as the illusory sense of movement or orientation	Pregnant, contraindication to medication, already taking drugs (last 24 h), or diagnosed stroke	No statistically significant difference in outcomes
Ercin et al,[25] 2021	Turkey	Double blind	200	None specified	Dimenhydrinate (50 mg) vs metoclopramide (10 mg) (IV)	Change in vertigo and nausea VAS score at 30 min	Adults in ED with vertigo defined as illusory sense of movement of orientation and rated at least 4 of 10 on VAS for associated nausea	Pregnancy, psychiatric or neurologic disorder, hemorrhage, or contraindication to study medications	No statistically significant differences in improvement in vertigo or nausea or changes in vital signs
İnan et al,[26] 2019	Turkey	Open label	64	BPPV	Epley repositioning maneuvers alone vs with betahistine (24 mg) (orally) twice daily or dimenhydrinate (50 mg) daily	Change in Dizziness Handicap Inventory at 10 d	Adults diagnosed with BPPV with the Dix-Hallpike maneuver	Previous ear surgery, cervical spine disease, Meniere disease, central vertigo, or carotid stenosis	Similar decrease in Dizziness Handicap Inventory scores in all 3 groups
Irving et al,[27] 2002	US	Double blind	40	Peripheral	Droperidol (2.5 mg) vs dimenhydrinate (50 mg) (IM)	Change in VAS scores at 30 min, "well enough to go home"	Patients in the ED aged 18-65 y, consistent with peripheral vertigo defined as the sensation of spinning, worse with movement and sudden in onset	Syncope, pregnancy, contraindication to study medications, taking similar medications, or concern for central or cardiac cause	No difference in any outcomes
Kim et al,[28] 2014	South Korea	Both	138	Idiopathic BPPV; all received Epley repositioning	Epley alone vs with dimenhydrinate (25 mg) (orally) twice daily for a week	Residual symptoms (yes or no) at 1 wk; presence of nystagmus	Diagnosis of BPPV after bedside examination and video nystagmography; resolution with Epley (or other) repositioning; no current medications	History of inner-ear issue or surgery, psychiatric issues, failure to resolve with Epley repositioning, or >2 canals involved	Control groups had significantly more residual symptoms at 1 wk
Marill et al,[29] 2000	US	Double blind	74	None specified; probably all-comers	Dimenhydrinate (50 mg) vs lorazepam (2 mg) (IV)	Decrease in average 10-point VAS score for vertigo at 1 and 2 h; measured multiple positions	Adults in the ED with vertigo defined as "hallucination of motion of self or surroundings"	Pregnancy or contraindications to study medications	Dimenhydrinate "more effective and less sedating"

Table 2. Randomized Clinical Trials Included in the Systematic Review (continued)

Source	Country	Blind or open label	No. of patients	Vertigo type	Medications, controls, and comparators	Main outcomes reported	Inclusion criteria	Main exclusion criteria	Main results
McClure et al,[30] 1980	Canada	Double blind	20	BPPV	Lorazepam (1 mg) vs diazepam (5 mg) vs placebo (orally) 3 times/d	10-point VAS score for dizziness, with 10 being starting point and 0 being complete resolution at 1, 2, 3, and 4 wk	"Classical" BPPV with nystagmus on Dix-Hallpike testing	Not BPPV	No difference in improvement
Ozdemir et al,[31] 2013	Turkey	Double blind	200	Peripheral	Dimenhydrinate (50 mg) vs piracetam (1000 mg) (IV)	100-point VAS scores initially and after treatment; need for additional dose (of same medication); dizziness, drowsiness, or weakness	Aged 18-70 y, with chief complaint of vertigo and "diagnosed with peripheral vertigo"	Age >70 y, pregnancy, contraindication to study medications, or any dangerous cause of vertigo (cardiac, anemia, poisoning, etc)	No difference in efficacy; fewer minor adverse events with piracetam
Perelló et al,[32] 1998	Spain	Double blind	110	Generic	Dotarizine (50 mg) vs cinnarizine (75 mg) (orally) twice daily	Complete resolution (no episodes) at 15, 30, 45, and 60 d; improvement at 60 d; normal daily activity after 60 d; rated as "very satisfactory" by investigator and by patient; side effects	Vertigo with nystagmus or abnormal vestibular tests	Pregnant, treated with medications for vertigo in the last 15 d, contraindication to study medications, ear surgery or trauma/acoustic neuroma, neurologic deficits, nonhorizontal nystagmus, alcohol abuse, or "severe metabolic diseases"	Dotarizine better than cinnarizine in multiple vertigo measures
Philipszoon et al,[33] 1961	Netherlands	Double blind	55	Multiple types	Cinnarizine (30 mg) vs placebo (orally) daily	"Benefit" at 1 week (yes or no); presence of inducible nystagmus (yes or no); side effects	"Complained of vertigo"; no other criteria listed	Not stated	Cinnarizine better than placebo at improving vertigo
Saberi et al,[34] 2019	Iran	Double blind	170	Acute peripheral, not BPPV	Promethazine (25 mg) (IM) vs ondansetron (4 mg) (IV)	Vertigo VAS score at 30 and 120 min as mean (SD); nausea VAS as well; side effects; need for rescue (readministration); mean relief score ranging from −6 to 9	Aged 20-60 y, with vertigo defined as a true sense of rotation or movement	New neurologic deficits, BPPV, contraindication to medications, recent head trauma, or use of any CNS depressants	Promethazine improved vertigo more; ondansetron improved nausea more
Shih et al,[35] 2017	US	Double blind	40	Peripheral	Diazepam (5 mg) vs meclizine (25 mg) (orally)	Change in 100-point VAS at 30 and 60 min, reported as mean change	Age 18-65 y; peripheral vertigo as diagnosed by an emergency physician	Mild vertigo (<40 on VAS), required parenteral therapy, pregnant, taking medications or sedatives, focal neurologic findings, or central or cardiovascular cause of vertigo	No significant differences in improvement
Sundararajan et al,[36] 2011	India	Open label	51	BPPV	Epley alone vs with cinnarizine (25 mg) (orally) 3 times daily	Cured, 50% cured, no improvement, or worse at 1 and 4 wk	Diagnosed with BPPV per diagnostic criteria including positive Dix-Hallpike in ED or ENT clinic	"Severe neck problems," recent stroke, retinal detachment, or uncontrolled hypertension	Control group did better than treatment group
Zhang et al,[37] 2012	China	Open label	84	BPPV	Epley alone vs with flunarizine (10 mg) daily, betahistine (12 mg) twice daily, and *Ginkgo biloba* (Ginaton) drops twice daily	Cure, effective, or ineffective at 7 and 28 d; recurrence rate at 1.5 y	Diagnosed with BPPV per criteria put forth by the Chinese Society of Otolaryngology; positive Dix-Hallpike test result; seen at ENT clinic	None specified	Average cure time with 18-d treatment: 39 d for control; more cure and more "effective" at 7 and 28 d with treatment

Source	Antihistamines VAS, mean (SD)	Antihistamines Total, No.	Controls VAS, mean (SD)	Controls Total, No.	Mean VAS difference (95% CI)	Weight, %
Antihistamines vs benzodiazepines						
Amini et al,[21] 2014	46.5 (18.2)	92	25.7 (15.3)	92	20.80 (15.94 to 25.66)	17.8
Marill et al,[29] 2000	38.0 (29.8)	37	23.2 (32.8)	37	14.80 (0.52 to 29.08)	12.3
Shih et al,[35] 2017	40.2 (24.2)	20	35.9 (30.2)	20	4.30 (-12.66 to 21.26)	10.8
Subtotal		**149**		**149**	**16.09 (7.18 to 25.01)**	**40.8**
Heterogeneity: $\tau^2 = 30.95$; $\chi^2_2 = 3.74$; $P = .15$; $I^2 = 47\%$						
Test for overall effect: $z = 3.54$; $P < .001$						
Antihistamines vs nonbenzodiazepine active controls						
Doğan et al,[24] 2015	29.2 (31.1)	47	37.5 (34.0)	47	-8.30 (-21.47 to 4.87)	13.0
Ercin et al,[25] 2021	51.4 (22.5)	100	49.9 (22.0)	100	1.50 (-4.67 to 7.67)	17.2
Irving et al,[27] 2002	33.0 (22.8)	20	33.0 (22.8)	20	0 (-14.13 to 14.13)	12.4
Saberi et al,[34] 2019	43.8 (23.0)	85	30.6 (24.1)	85	13.20 (6.12 to 20.28)	16.7
Subtotal		**252**		**252**	**2.72 (-6.07 to 11.51)**	**59.2**
Heterogeneity: $\tau^2 = 54.52$; $\chi^2_3 = 10.72$; $P = .01$; $I^2 = 72\%$						
Test for overall effect: $z = 0.61$; $P = .54$						
Total		**401**		**401**	**7.36 (-1.12 to 15.84)**	**100**
Heterogeneity: $\tau^2 = 99.14$; $\chi^2_6 = 36.51$; $P < .001$; $I^2 = 84\%$						
Test for overall effect: $z = 1.70$; $P = .09$						
Test for subgroup differences: $\chi^2_1 = 4.38$; $P = .04$; $I^2 = 77.2\%$						



Key Points

Question Are benzodiazepines or antihistamines effective in the treatment of acute vertigo?

Findings In this systematic review and meta-analysis of 17 trials involving 1586 participants, 7 studies comprising 802 total patients evaluated the primary outcome of change in 100-point vertigo visual analog scale scores at approximately 2 hours after treatment with an antihistamine or benzodiazepine. Antihistamines resulted in greater patient improvement than benzodiazepines (difference, 16.1) but were not superior to other active comparators, including ondansetron, droperidol, metoclopramide, and piracetam.

Meaning The findings of this study suggest that antihistamines may be superior to benzodiazepines in the treatment of acute vertigo and that the use of the latter should be discouraged.

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RESEARCH

Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis

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Objective

To evaluate the effectiveness and safety of viscosupplementation for pain and function in patients with knee osteoarthritis.

Eligibility criteria for study selection

Randomised trials comparing viscosupplementation
with placebo or no intervention for knee osteoarthritis treatment.

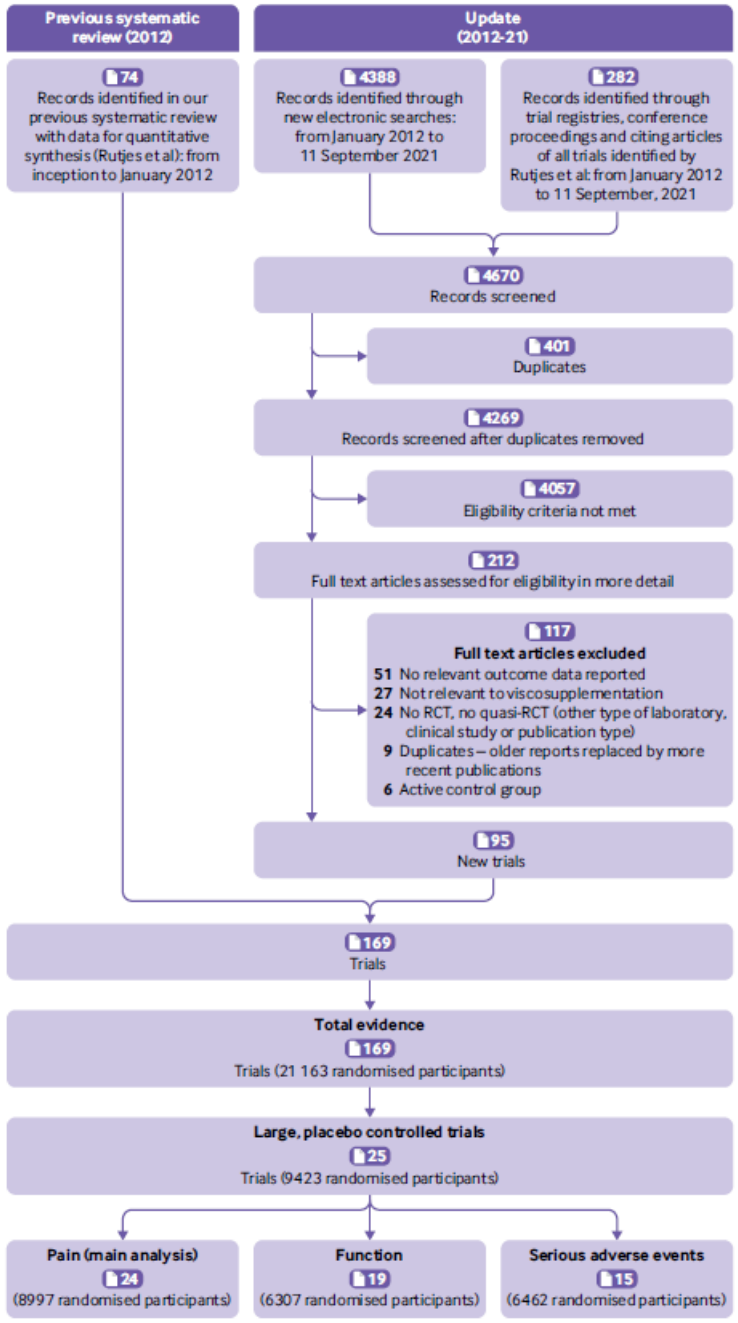


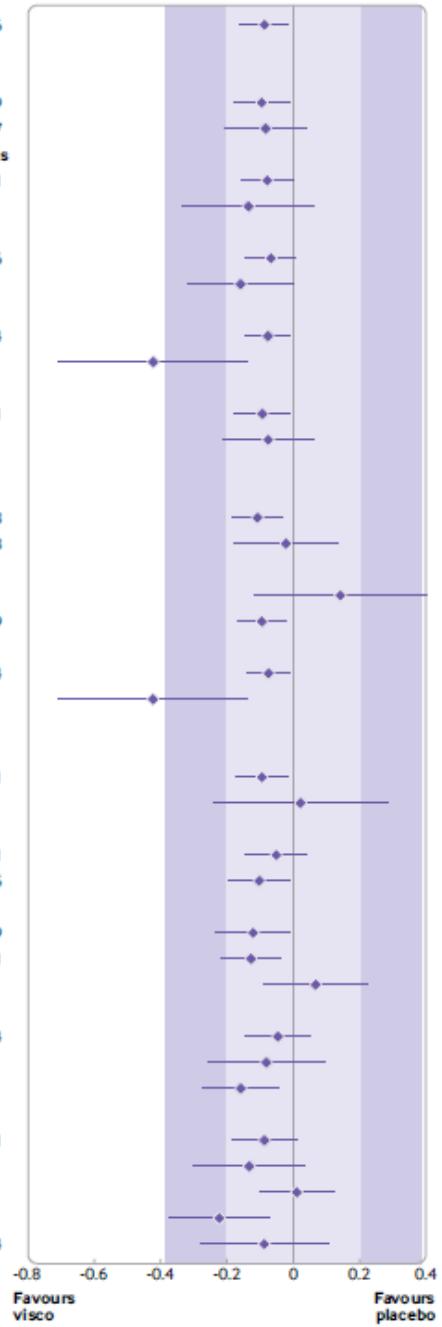
Fig 1 | Flowchart showing steps in the selection of relevant trials. RCT=randomised controlled trial

Table 1 | Characteristics of the 25 large, placebo controlled trials*

Author (year)	No of randomised participants		Instrument		Reported SAEs	Publication status	Funding independent of industry	Molecular weight	Structure	No of injections (cycles)†
	Visco	Placebo	Pain	Function						
Shichikawa (1983)[34]	114	114	Global pain (VAS)	—	No	Published	No	Unclear	Non-cross linked	5 (1)
Puhl (1993)[35]	102	107	Global pain (VAS)	Lequesne index	No	Published	No	Low	Non-cross linked	5 (1)
Lohmander (1996)[36]	120	120	Global pain (VAS)	Lequesne index	No	Published	No	Low	Non-cross linked	5 (1)
Altman and Moskowitz (1998)[37]	164	168	Pain on walking (VAS)	WOMAC function	Yes	Published	No	Low	Non-cross linked	5 (1)
Brandt (2001)[38]‡	114	112	—	—	Yes	Published	No	Intermediate	Non-cross linked	3 (1)
Seikagaku [UK] (2001)[39]	116	115	Lesquene index	Lequesne index	No	Unpublished	No	Low	Non-cross linked	5 (1)
Jubb (2003)[40]	208	200	Pain on walking (VAS)	—	Yes	Published	No	Low	Non-cross linked	3 (3)
Altman (2004)[41]	173	174	WOMAC pain	WOMAC function	Yes	Published	No	High	Cross linked	1 (1)
Day (2004)[42]	116	124	WOMAC pain	WOMAC function	No	Published	No	Low	Non-cross linked	5 (1)
Pham (2004)[43]	131	85	Global pain (VAS)	Lequesne index	No	Published	No	Intermediate	Unclear	3 (3)
Altman (2009)[44]	293	295	Pain on walking (VAS)	WOMAC function	Yes	Published	No	Intermediate	Non-cross linked	3 (1)
Baltzer (2009)[45]	135	107	Global pain (VAS)	WOMAC function	No	Published	Yes	Low	Non-cross linked	3 (1)
Chevalier (2010)[46]	124	129	WOMAC pain	WOMAC function	Yes	Published	No	High	Cross linked	1 (1)
Jørgensen (2010)[47]	167	170	Pain on walking (VAS)	Lequesne index	No	Published	No	Low	Non-cross linked	5 (1)
Huang (2011)[48]	100	100	Pain on walking (VAS)	WOMAC function	Yes	Published	No	Low	Non-cross linked	5 (1)
Strand (2012)[49]	251	128	WOMAC pain	WOMAC function	Yes	Published	No	Unclear	Cross linked	1 (1)
NCT00988091 (2012)[50]	298	298	Pain on walking (VAS)	WOMAC function	Yes	Unpublished	No	Unclear	Unclear	1 (1)
Arden (2014)[51]	108	110	WOMAC pain	WOMAC function	No	Published	No	High	Cross linked	1 (1)
NCT01372475 (2015)[52]	400	400	WOMAC pain	—	No	Unpublished	No	Unclear	Non-cross linked	2 (1)
NCT01934218 (2017)[53]§	404	410	Pain on walking (VAS)	—	Yes	Unpublished	No	Unclear	Cross linked	1 (1)
Hangody (2017)[54]	150	69	WOMAC pain	WOMAC function	Yes	Published	No	Intermediate	Cross linked	1 (1)
Petterson and Plantcher (2018)[55]	184	185	Patient global assessment (VAS)	WOMAC function	Yes	Published	No	Intermediate	Cross linked	1 (1)
NCT02495857 (2018)[56]¶	400	199	WOMAC pain	WOMAC function	Yes	Unpublished	No	Intermediate	Non-cross linked	3 (1)
Ke (2021)[57]	220	220	WOMAC pain	—	Yes	Published	No	High	Cross linked	1 (1)
Migliore (2021)[58]	347	345	Global pain (VAS)	Lequesne index	Yes	Published	No	High and low	Unclear	1 (1)

Main and subgroup analysis for PAIN

Variable	No of trials	No of patients (visco/placebo)	Standardised mean difference (95% CI)	τ^2	P value
All trials	24	4466/4236	-0.08 (-0.15 to -0.02)	0.02	
Trial design					
Bias in randomisation process					
Low risk	12	2587/2359	-0.09 (-0.17 to -0.02)	0.01	0.80
High risk/some concerns	12	1879/1877	-0.08 (-0.20 to 0.04)	0.03	
Bias due to deviations from intended interventions					
Low risk	19	3935/3711	-0.08 (-0.15 to -0.00)	0.02	0.57
High risk/some concerns	5	531/525	-0.13 (-0.33 to 0.07)	0.03	
Bias due to missing outcome data					
Low risk	18	3644/3416	-0.06 (-0.14 to 0.01)	0.01	0.27
High risk/some concerns	6	822/820	-0.16 (-0.32 to 0.00)	0.02	
Bias in measurement of outcome					
Low risk	23	4370/4134	-0.07 (-0.14 to -0.01)	0.01	0.02
High risk/some concerns	1	96/102	-0.42 (-0.70 to -0.14)		
Bias due to selection of reported result					
Low risk	16	3480/3311	-0.09 (-0.17 to -0.01)	0.02	0.85
High risk/some concerns	8	986/925	-0.07 (-0.21 to 0.06)	0.02	
Publication characteristics					
Publication status					
Published	19	3073/2838	-0.11 (-0.18 to -0.03)	0.01	0.26
Unpublished	5	1393/1398	-0.02 (-0.17 to 0.13)	0.02	
Funding independent of industry					
Yes	1	135/107	0.14 (-0.11 to 0.40)		0.20
No/unclear	23	4331/4129	-0.09 (-0.16 to -0.02)	0.02	
Language of publication					
English	23	4370/4134	-0.07 (-0.14 to -0.01)	0.01	0.02
Others	1	96/102	-0.42 (-0.70 to -0.14)		
Intervention characteristics					
No of cycles					
1	22	4127/3951	-0.09 (-0.17 to -0.02)	0.02	0.37
>1	2	339/285	0.02 (-0.24 to 0.28)	0.02	
Structure					
Cross linked	8	1600/1421	-0.05 (-0.14 to 0.04)	0.01	0.56
Non-cross linked/unclear	16	2866/2815	-0.10 (-0.19 to -0.01)	0.02	
Follow-up (months)					
<3 months	9	1568/1509	-0.12 (-0.23 to -0.01)	0.02	0.08
3-6 months	11	1862/1741	-0.12 (-0.21 to -0.04)	0.01	
>6 months	4	1036/986	0.07 (-0.08 to 0.22)	0.02	
No of injections					
1 or 2	11	2629/2444	-0.04 (-0.14 to 0.05)	0.02	0.38
3	5	952/876	-0.08 (-0.25 to 0.10)	0.03	
>3	8	885/916	-0.15 (-0.27 to -0.04)	0.01	
Molecular weight					
Low	9	1132/1121	-0.08 (-0.18 to 0.01)	0.00	0.70
Intermediate	5	940/822	-0.13 (-0.30 to 0.04)	0.02	
High	4	620/633	0.01 (-0.10 to 0.12)	0.00	
Low and high	1	341/336	-0.22 (-0.37 to -0.07)		
Unclear	5	1433/1324	-0.08 (-0.27 to 0.10)	0.04	



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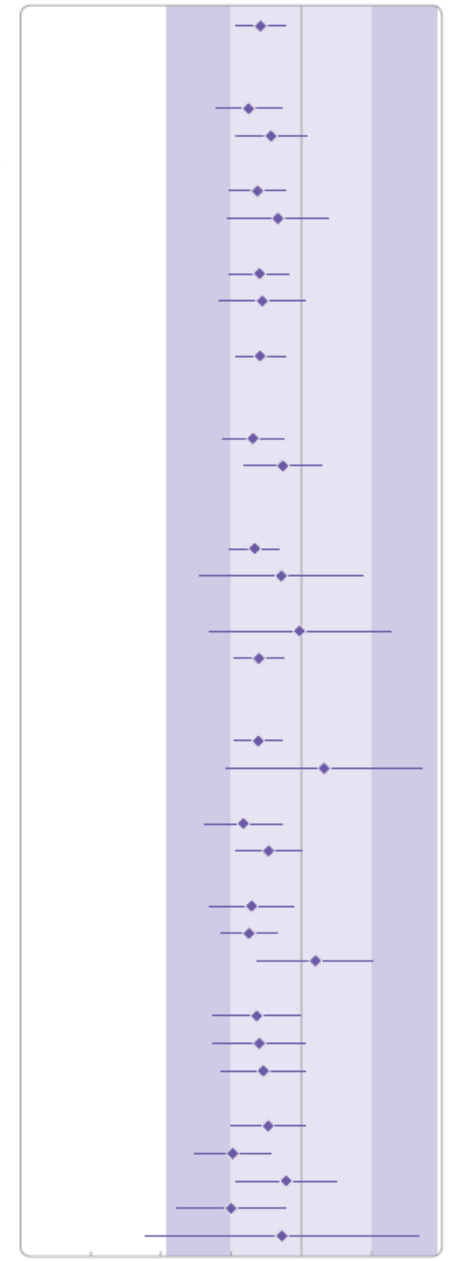
Main and subgroup analysis for FUNCTION

Variable	No of trials	No of patients (visco/placebo)	Standardised mean difference (95% CI)	τ^2	P value
All trials	19	3175/2933	-0.11 (-0.18 to -0.05)	0.01	
Trial design					
Bias in randomisation process					
Low risk	9	1588/1359	-0.15 (-0.24 to -0.06)	0.01	0.36
High risk/some concerns	10	1587/1574	-0.08 (-0.18 to 0.02)	0.01	
Bias due to deviations from intended interventions					
Low risk	15	2720/2491	-0.13 (-0.20 to -0.05)	0.01	0.52
High risk/some concerns	4	455/442	-0.06 (-0.21 to 0.08)	0.00	
Bias due to missing outcome data					
Low risk	14	2429/2196	-0.12 (-0.20 to -0.03)	0.01	0.88
High risk/some concerns	5	746/737	-0.11 (-0.23 to 0.01)	0.00	
Bias in measurement of outcome					
Low risk	19	3175/2933	-0.11 (-0.18 to -0.05)	0.01	
High risk/some concerns	-	-			
Bias due to selection of reported result					
Low risk	13	2473/2291	-0.14 (-0.22 to -0.05)	0.01	0.33
High risk/some concerns	6	702/642	-0.05 (-0.16 to 0.05)	0.00	
Publication characteristics					
Publication status					
Published	16	2573/2335	-0.13 (-0.20 to -0.06)	0.01	0.33
Unpublished	3	602/598	-0.06 (-0.28 to 0.17)	0.03	
Funding independent of industry					
Yes	1	135/107	-0.00 (-0.26 to 0.25)		0.49
No/unclear	18	3040/2826	-0.12 (-0.19 to -0.05)	0.01	
Intervention characteristics					
No of cycles					
1	18	3044/2848	-0.12 (-0.19 to -0.05)	0.01	0.28
>1	1	131/85	0.07 (-0.21 to 0.34)		
Structure					
Cross linked	6	982/794	-0.16 (-0.27 to -0.05)	0.01	0.35
Non-cross linked/unclear	13	2193/2139	-0.09 (-0.18 to -0.01)	0.01	
Follow-up (months)					
<3 months	6	1040/969	-0.14 (-0.26 to -0.02)	0.01	0.11
3-6 months	10	1585/1456	-0.15 (-0.23 to -0.07)	0.00	
>6 months	3	550/508	0.04 (-0.12 to 0.20)	0.01	
No of injections					
1 or 2	8	1618/1424	-0.12 (-0.24 to -0.00)	0.02	0.99
3	4	748/676	-0.12 (-0.25 to 0.01)	0.00	
>3	7	809/833	-0.11 (-0.22 to 0.01)	0.01	
Molecular weight					
Low	8	944/940	-0.09 (-0.20 to 0.01)	0.00	0.50
Intermediate	5	944/822	-0.20 (-0.30 to -0.09)	0.00	
High	3	404/413	-0.04 (-0.18 to 0.10)	0.00	
Low and high	1	341/336	-0.20 (-0.35 to -0.05)		
Unclear	2	542/422	-0.05 (-0.44 to 0.33)	0.07	



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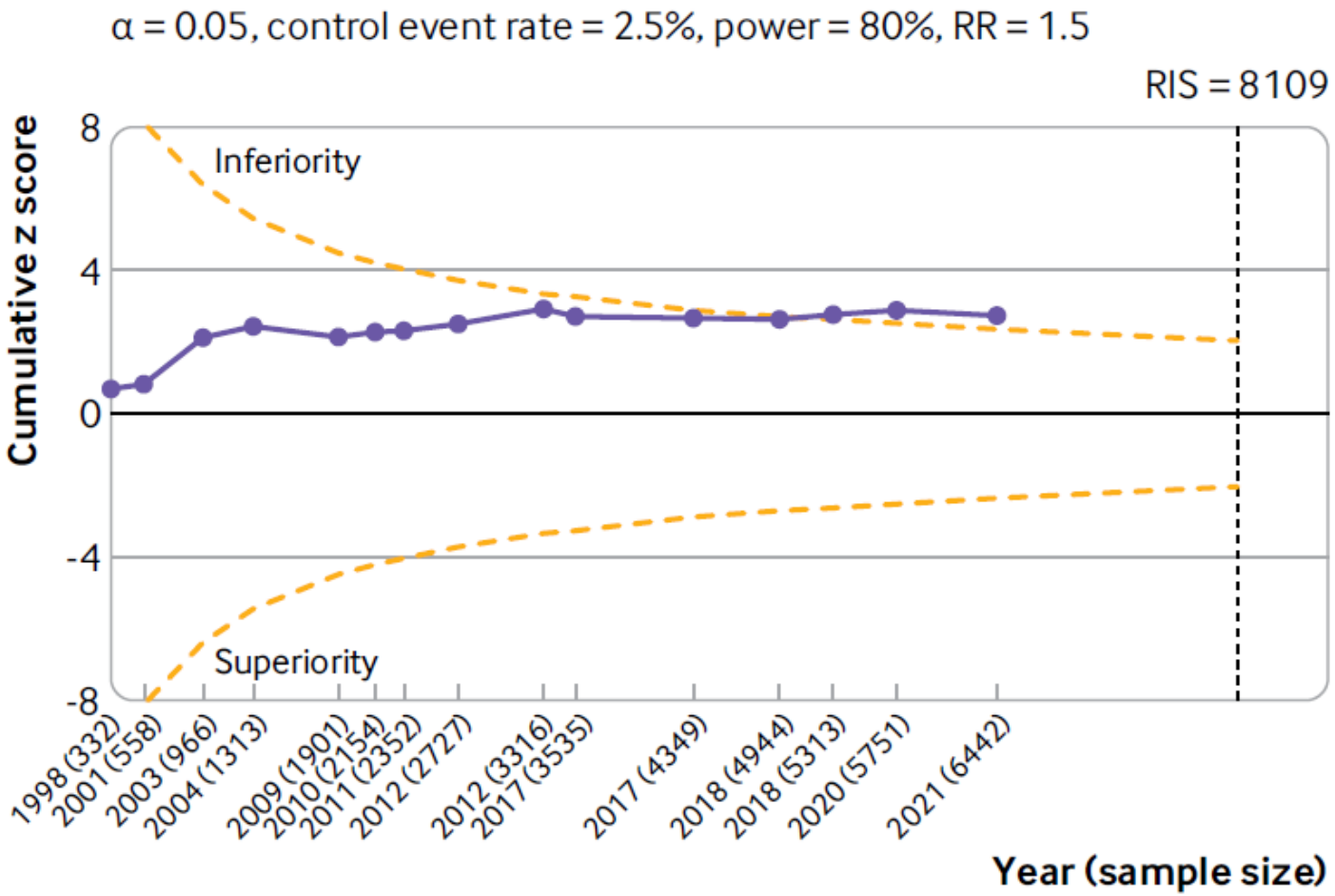
The significantly higher rate of **serious adverse events** in patients receiving viscosupplementation compared with those receiving placebo is a robust finding.



PEREIRA TV, ET AL.
BMJ 2022;378:E069722

WHAT IS ALREADY KNOWN ON THIS TOPIC

Intra-articular injections of hyaluronic derivatives (viscosupplementation) have been used to treat knee osteoarthritis for over 50 years

The effectiveness and safety of this treatment are still a topic of debate

Emerging evidence indicates that treatment effects could be smaller than previously reported

WHAT THIS STUDY ADDS

Strong conclusive evidence indicates that viscosupplementation leads to a small reduction in knee osteoarthritis pain compared with placebo, but the difference is less than the minimal clinically important between group difference

Strong conclusive evidence also indicates that viscosupplementation increases the risk of serious adverse events compared with placebo

The findings do not support broad use of viscosupplementation to treat knee osteoarthritis

PEREIRA TV, ET AL.
BMJ 2022;378:E069722

RESEARCH

Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data

Michèle Bally,[1,2] Nandini Dendukuri,[3,4] Benjamin Rich,[4] Lyne Nadeau,[4] Arja Helin-Salmivaara,[5] Edeltraut Garbe,[6] James M Brophy[2,4,7]

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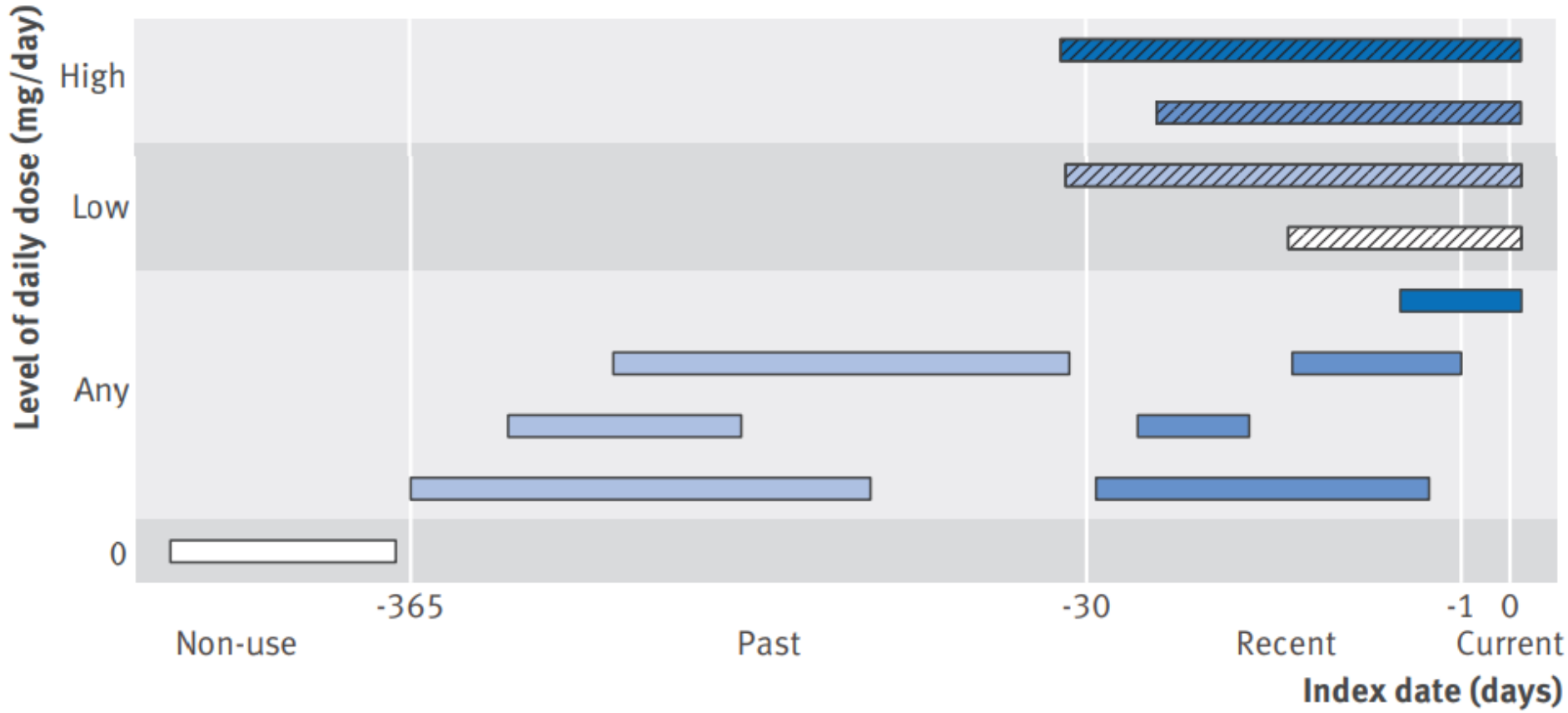


- Non-use
- Past use at any dose
- Recent use at any dose
- Current use at any dose for 1-7 days
- Current use at low dose for 8-30 days
- Current use at low dose for ›30 days
- Current use at high dose for 8-30 days
- Current use at high dose for ›30 days

Celecoxib (low dose ≤200 mg, high dose ›200 mg)
Diclofenac (low dose ≤100 mg, high dose ›100 mg)
Ibuprofen (low dose ≤1200 mg, high dose ›1200 mg)
Naproxen (low dose ≤750 mg, high dose ›750 mg)

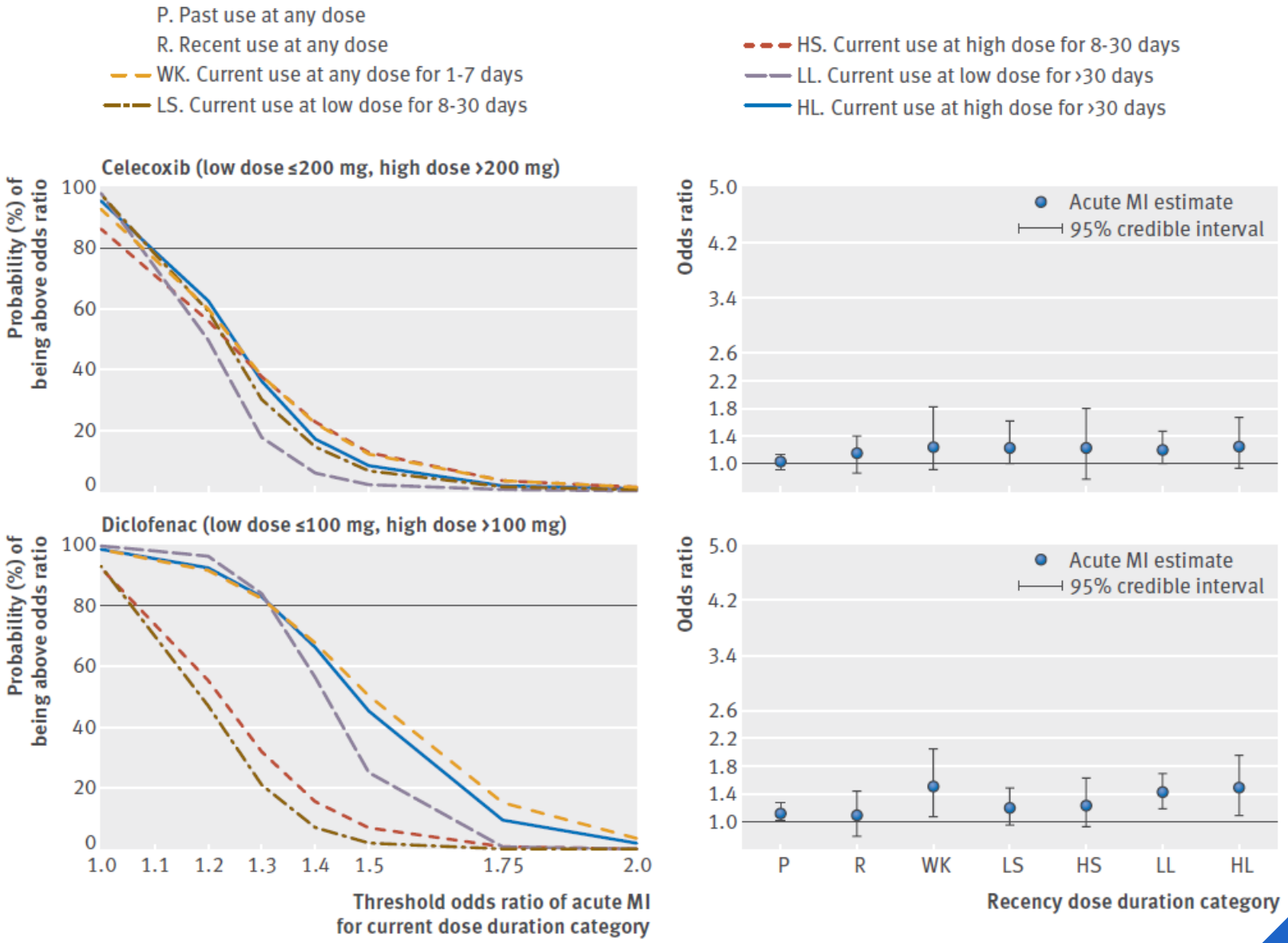
BALLY M, ET AL.
BMJ 2017;357:J1909

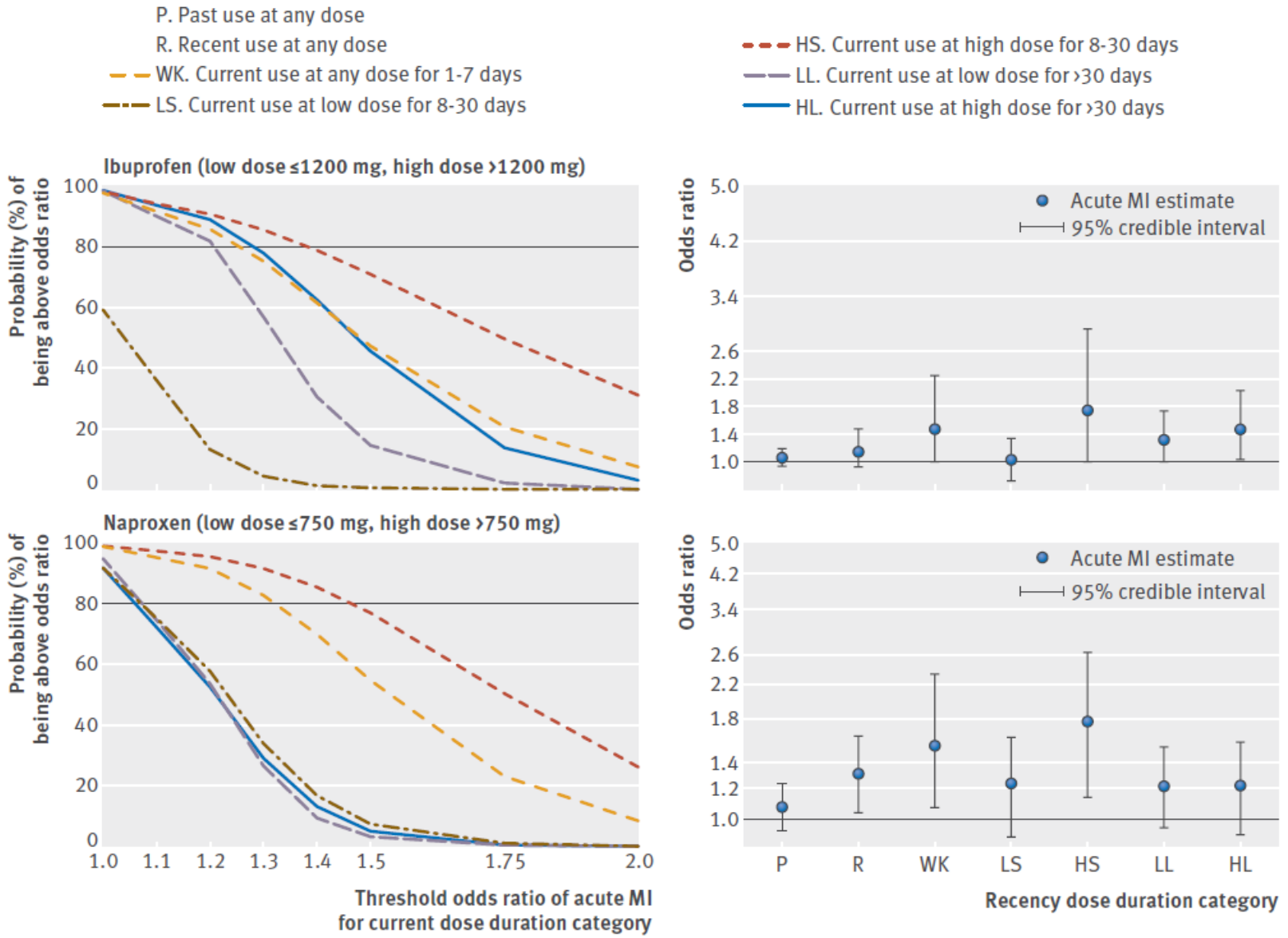
Table 1 | Prevalence of confounders for association between exposure to non-steroidal anti-inflammatory drugs and acute myocardial infarction outcome at index date documented in each healthcare database study. Values are numbers (percentages) unless stated otherwise

Confounders	RAMQ (n=233 816)	Finland (n=172 219)	GPRD (n=17 561)	Saskatchewan (n=23 167)
Mean (SD) age at index date (years)	77.8 (6.1)	68.9 (12.7)	70.2 (11.5)	58.1 (12.8)
Median (interquartile range) age at index date (years)	78 (73-83)	70 (60-78)	71 (62-79)	56 (47-69)
Male sex	118 492 (50.7)	107 225 (62.3)	10 349 (58.9)	11 831 (51.1)
Comorbidities:				
Diabetes	40 812 (17.5)	12 911 (7.5)	1933 (11.0)	1663 (7.2)
Hyperlipidaemia	72 008 (30.8)	19 212 (11.2)	2397 (13.7)	6738 (29.1)
Hypertension	108 916 (46.6)	44 702 (26.0)	5944 (33.9)	9181 (39.6)
Previous myocardial infarction	17 025 (7.3)	NA	NA	1154 (5.0)
Coronary heart disease	79 466 (34.0)	29 998 (17.4)	3731 (21.3)	4972 (21.5)
Congestive heart failure	19 602 (8.4)	NA	NA	1722 (7.4)
Cerebrovascular disease	22 203 (9.5)	NA	1480 (8.4)	1798 (7.8)
Peripheral vascular disease	15 833 (6.8)	NA	NA	706 (3.1)
Chronic obstructive pulmonary disease	53 465 (22.9)	NA	NA	2546 (11.0)
Gastrointestinal ulcer disease	68 062 (29.1)	NA	NA	9419 (40.7)
Gastrointestinal bleed	5686 (2.4)	NA	NA	1039 (4.5)
Acute or chronic renal failure	4102 (1.8)	NA	NA	148 (0.6)
Rheumatoid arthritis	4245 (1.8)	5180 (3.0)	574 (3.3)	1277 (5.5)
Concomitant drug treatment:				
Oral corticosteroids	5301 (2.3)	NA	NA	NA
Clopidogrel	4007 (1.7)	172 (0.1)	NA	NA
Cardioprotective aspirin	53738 (23.0)	NA	NA	NA

NA=systematically missing in original study.

Fig 2 | Plot of probability of % credible interval exceeding odds ratios of acute myocardial infarction (MI) for exposure categories corresponding to current use for each non-steroidal anti-inflammatory drug (NSAI D) versus non-use and corresponding forest plot for risk of acute myocardial infarction for each exposure category in pooled studies





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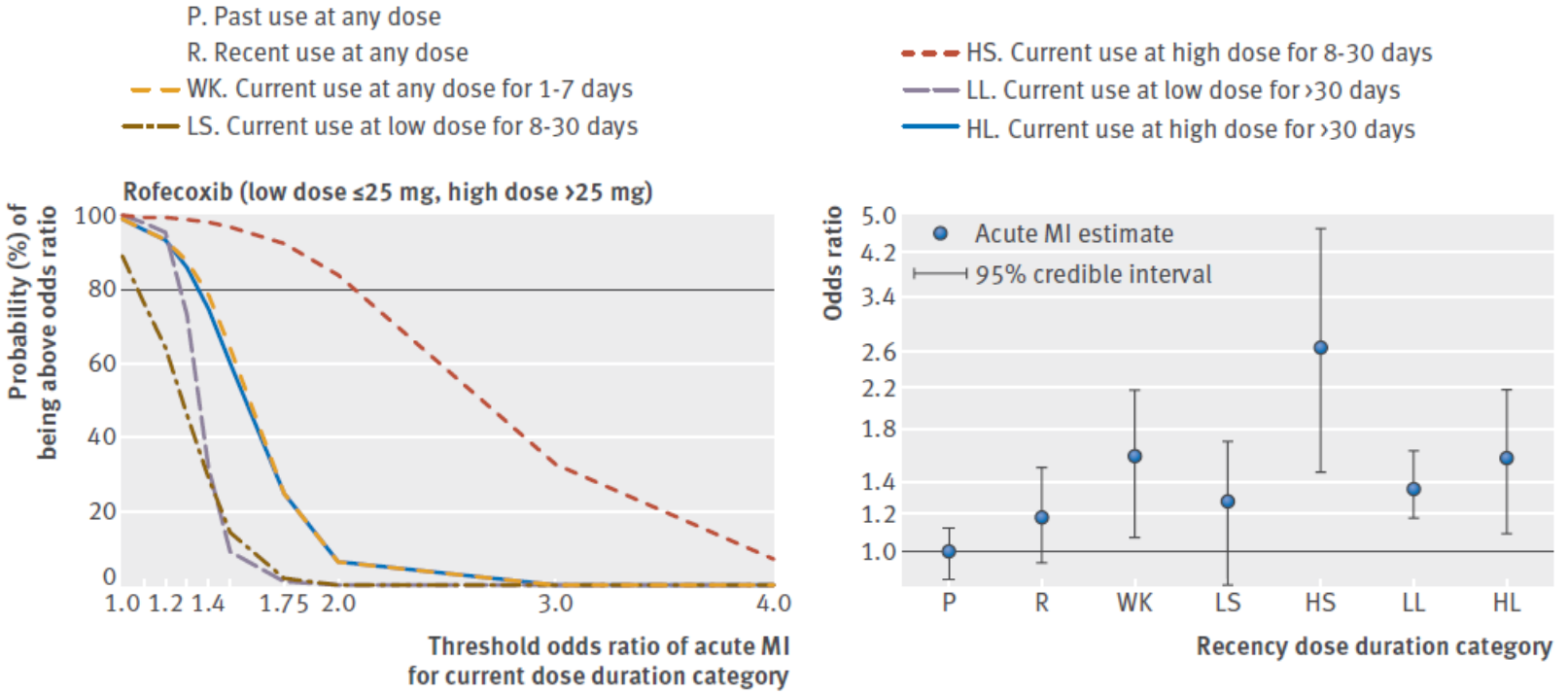

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BMJ 2017;357:J1909

WHAT IS ALREADY KNOWN ON THIS TOPIC

Evidence suggests that both traditional and cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) can increase the risk of acute myocardial infarction

The timing of the risk, the effect of dose, treatment duration, and the comparative risks between NSAIDs are poorly understood

WHAT THIS STUDY ADDS

Using a bayesian meta-analysis of individual patient data and studying real world settings, it is shown that all traditional NSAIDs, including naproxen, appear to be associated with an increased risk of acute myocardial infarction

The risk with celecoxib does not seem to be greater than that with traditional NSAIDs. Onset of risk occurs in the first week

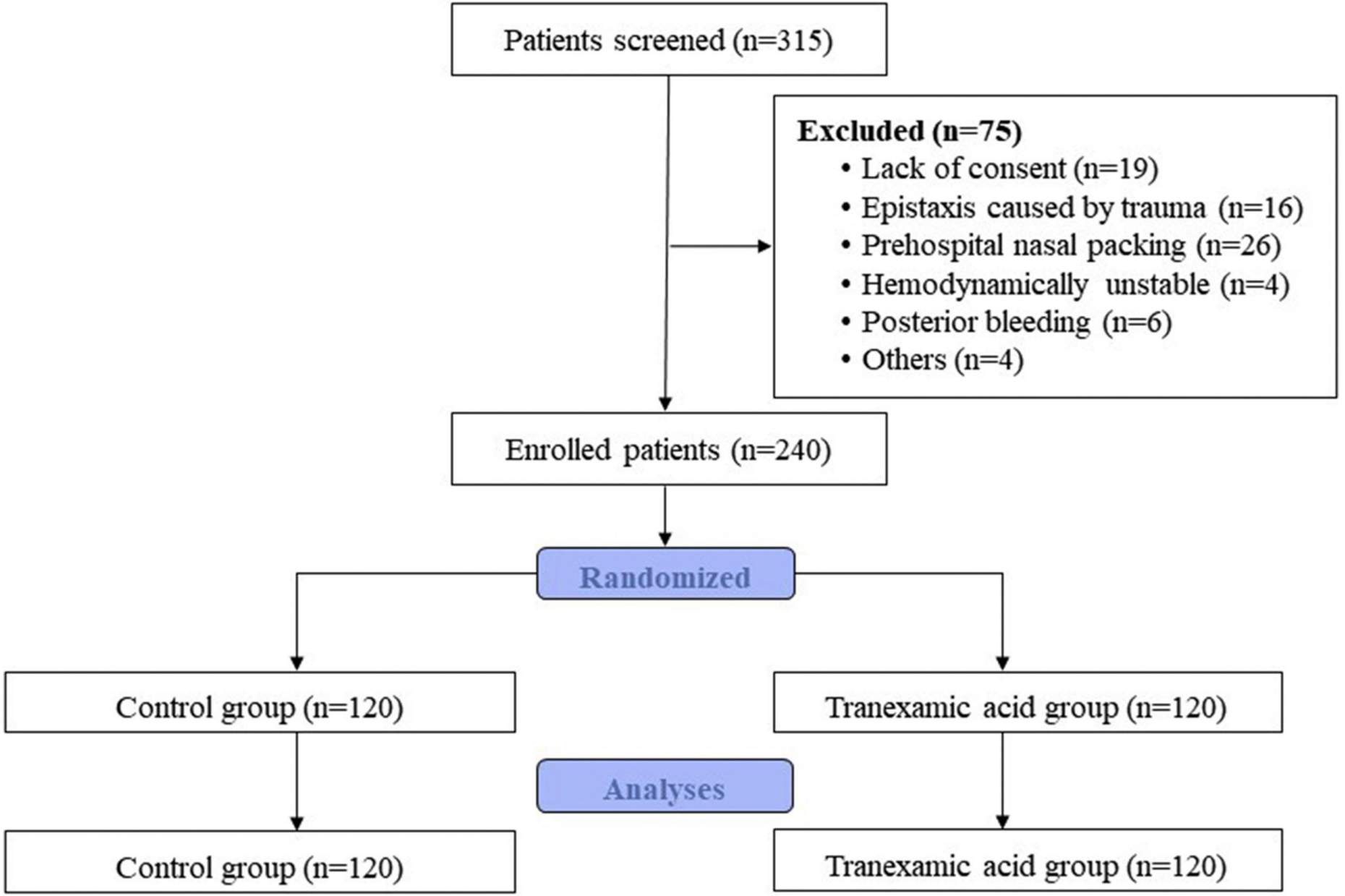
Short term use for 8-30 days at a high daily dose (celecoxib >200 mg, diclofenac >100 mg, ibuprofen >1200 mg, and naproxen >750 mg) is associated with the greatest harms, without obvious further increases in risk beyond the first 30 days

BALLY M, ET AL.
BMJ 2017;357:J1909

GENERAL MEDICINE/ORIGINAL RESEARCH

Intranasal Topical Application of Tranexamic Acid in Atraumatic Anterior Epistaxis: A Double-Blind Randomized Clinical Trial

Milad Hosseinialhashemi, MD; Reza Jahangiri, MD*; Ali Faramarzi, MD; Naeimehossadat Asmarian, PhD; Sarvin Sajedianfard, MD; Maryam Kherad, MD; Amir Soltaniesmaeili, MD; Amirhossein Babaei, MD, MPH



HOSSEINIALHASHEMI M, ET AL.
ANN EMERG MED. 2022;80(3):182-188

Table 1. Baseline characteristics of participants stratified by study arm.*

Variable	Treatment Group (n=120)	Control Group (n=120)
Male sex	66 (55.0%)	60 (50.0%)
Age, y	52 (43-61)	53 (46-63)
Systolic blood pressure, mmHg	135 (125-140)	130 (125-140)
Diastolic blood pressure, mmHg	75 (75-84)	75 (75-80)
Aspirin consumption	33 (27.5%)	40 (33.3%)

*Values are presented as either n (%) or median (interquartile range).

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Table 2. Frequency (%) of clinical outcomes in the 2 study arms.

Variable	Tranexamic Acid (n=120)	Control Group (n=120)	Difference, %, (95% CI)	OR (95% CI)
Anterior nasal packing	60 (50.0%)	77 (64.2%)	14.2 (1.8-26.6)	0.56 (0.33-0.94)
More than 2 hours of stay in the ED	11 (9.2%)	25 (20.8%)	11.6 (2.8-20.6)	0.38 (0.18-0.82)
Rebleeding within 24 hours	18 (15.0%)	36 (30.0%)	15 (4.6-25.4)	0.41 (0.22-0.78)
Electrical cauterization	75 (62.5%)	81 (67.5%)	5 (−7.0 to 7.0)	0.80 (0.47-1.36)
Rebleeding within 1-7 days	9 (7.5%)	16 (13.3%)	5.8 (−1.9 to 13.5)	0.53 (0.22-1.25)

CI, Confidence interval; *OR,* odds ratio.

Editor's Capsule Summary

What is already known on this topic

Early data have suggested a possible benefit to topical tranexamic acid for epistaxis, but more recent data have found no benefit.

What question this study addressed

This was a randomized controlled trial of tranexamic acid for anterior nasal epistaxis used in conjunction with phenylephrine and lidocaine.

What this study adds to our knowledge

Tranexamic acid reduced rates of anterior nasal packing, emergency department stay of more than 2 hours, and rebleeding within 24 hours.

How this is relevant to clinical practice

Tranexamic acid reduces the need for anterior nasal packing and risk of rebleeding in patients not on anticoagulants. Clinicians should consider tranexamic acid as part of the management for anterior epistaxis.

HOSSEINIALHASHEMI M, ET AL.
ANN EMERG MED. 2022;80(3):182-188

Research

JAMA | Original Investigation

Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder

The PRIME Care Randomized Clinical Trial

David W. Oslin, MD; Kevin G. Lynch, PhD; Mei-Chiung Shih, PhD; Erin P. Ingram, BA; Laura O. Wray, PhD; Sara R. Chapman, MS, OTR/L; Henry R. Kranzler, MD; Joel Gelernter, MD; Jeffrey M. Pyne, MD; Annjanette Stone, BS; Scott L. DuVall, PhD; Lisa Soleymani Lehmann, MD, PhD, MSc; Michael E. Thase, MD; and the PRIME Care Research Group

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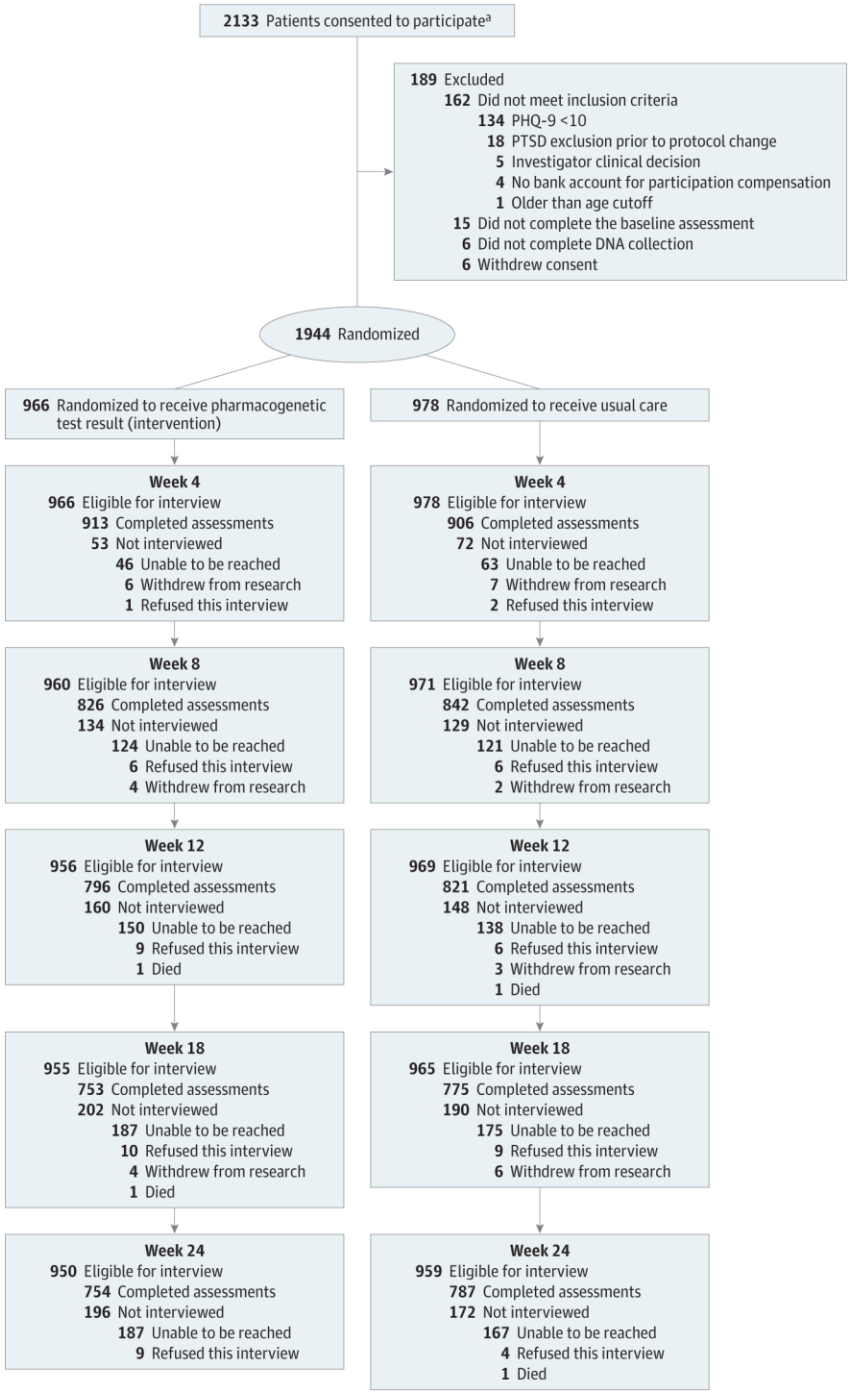

 OSLIN DW, ET AL.
JAMA. 2022;328(2):151-161

Table 2. Patient Baseline Demographics, Social, and Clinical Characteristics

Characteristic	Group, No. (%)	
	Pharmacogenomic guided	Usual care
No.	966	978
Patient characteristics		
Age, mean (SD), y	48 (15)	47 (15)
Sex		
Female	229 (24)	262 (27)
Male	737 (76)	716 (73)
Race		
African American/Black	185 (19)	167 (17)
Asian Pacific Islander	31 (3)	24 (3)
Native American/Alaskan	10 (1)	9 (1)
White	644 (67)	688 (70)
Other/mixed[a]	90 (9)	84 (9)
Refused	6 (1)	6 (1)
Hispanic ethnicity	113 (12)	104 (11)
Financial status		
Have just enough to get along	482 (50)	492 (50)
Are comfortable	338 (35)	352 (36)
Can't make ends meet	127 (13)	116 (12)
Clinical symptoms		
PHQ-9 score, inclusion criteria >9, mean (SD)[b]	17.5 (4.3)	17.5 (4.3)
Treatment refractory[c]	288 (30)	301 (31)
GAD-7 score, mean (SD)[d]	14.1 (4.8)	13.9 (5.0)
PTSD presence[e]	566 (59)	562 (58)
PCL-5 score in those with PTSD, mean (SD)[f]	51.5 (12.0)	51.8 (12.0)
Suicidal ideation (C-SSRS) (moderate or higher risk), No./total (%)[g]	187/597 (31)	190/596 (32)
Alcohol use		
Those with at-risk drinking[h]	219 (23)	230 (24)
Drinks per week, median (IQR)	0 (0-3)	0 (0-4)
Recent regular (last 3 mo) marijuana use[i]	227 (23)	238 (24)
Other recent regular (last 3 mo) drug use[i]	15 (2)	13 (1)
Current tobacco use[i]	256 (27)	250 (26)
VR-12 composite score, mean (SD)[j]		
Mental	23.8 (10.6)	24.9 (10.2)
Physical	37.9 (13.4)	36.4 (13.1)

INTERVENTIONS Results from a commercial pharmacogenomic test were given to clinicians in the pharmacogenomic-guided group (n = 966). The comparison group received usual care and access to pharmacogenomic results after 24 weeks (n = 978).

OSLIN DW, ET AL.
JAMA. 2022;328(2):151-161

Table 4. Effect of Immediate Return of Pharmacogenetic Results (Pharmacogenomic-Guided Group) vs Usual Care on Depression Remission, Response, and Symptom Improvement

	Group, No. (%)		Estimated within time point effect of intervention			Pooled effect of group over time		
	Pharmacogenomic guided	Usual care	RD, % (95% CI)	OR (95% CI)	*P* value	OR (95% CI)	RD (95% CI), %	*P* value
Remission (PHQ-9 ≤ 5)								
4 wk	86 (9.4)	72 (8.0)	1.5 (−1.2 to 4.1)	1.21 (0.82 to 1.59)	.27			
8 wk	121 (14.7)	95 (11.3)	3.6 (0.5 to 6.6)	1.38 (1.05 to 1.81)	.02			
12 wk	131 (16.5)	92 (11.2)	5.4 (2.2 to 8.6)	1.59 (1.21 to 2.10)	.001	1.28 (1.05 to 1.57)	2.8 (0.6 to 5.1)	.02
18 wk	119 (15.8)	105 (13.6)	2.4 (−0.8 to 5.5)	1.21 (0.94 to 1.57)	.14			
24 wk	130 (17.2)	126 (16.0)	1.5 (−2.4 to 5.3)	1.11 (0.84 to 1.47)	.45			
Response (>50% decrease in PHQ-9 total score)								
4 wk	158 (17.3)	149 (16.5)	0.9 (−2.3 to 4.0)	1.07 (0.85 to 1.34)	.58			
8 wk	216 (26.2)	176 (20.9)	5.5 (1.7 to 9.3)	1.36 (1.10 to 1.70)	.005			
12 wk	239 (30.0)	195 (23.8)	6.6 (2.1 to 11.0)	1.41 (1.12 to 1.77)	.004	1.25 (1.07 to 1.46)	4.0 (1.2 to 6.8)	.005
18 wk	214 (28.4)	204 (26.3)	2.4 (−1.6 to 6.4)	1.13 (0.92 to 1.39)	.23			
24 wk	242 (32.1)	216 (27.5)	5.1 (0.6 to 9.6)	1.29 (1.03 to 1.60)	.03			
	Mean (SD)		Mean difference (95% CI)			Difference (95% CI)		
Symptom improvement (decrease in PHQ-9 total score)								
4 wk	3.4 (5.0)	3.1 (4.9)	0.25 (−0.20 to 0.70)		.27			
8 wk	4.6 (5.6)	4.1 (5.1)	0.51 (0.03 to 1.00)		.04			
12 wk	5.3 (5.7)	4.4 (5.2)	0.96 (0.42 to 1.50)		<.001	0.56 (0.17 to 0.95)		.005
18 wk	5.1 (5.8)	4.7 (5.5)	0.47 (−0.05 to 1.00)		.08			
24 wk	5.4 (5.9)	4.8 (5.6)	0.65 (0.10 to 1.19)		.02			

Abbreviations: OR, odds ratio; PHQ-9, Patient Health Questionnaire–9; RD, risk difference.

JAMA®

QUESTION Does provision of pharmacogenomic testing for drug-gene interactions affect selection of antidepressant medication and response of depressive symptoms in patients with major depressive disorder (MDD)?

CONCLUSION This clinical trial found that in patients with MDD, pharmacogenomic testing for drug-gene interactions vs usual care reduced prescription of medications with predicted drug-gene interactions and had small and nonpersistent effects on remission of depressive symptoms.

POPULATION

1453 Men
491 Women

Adults with MDD who were initiating or switching treatment with a single antidepressant

Mean age: **48** years

LOCATIONS

22
Veterans Affairs medical centers in the US

INTERVENTION

1944 Patients randomized

966
Pharmacogenomic guided
Results from a commercial pharmacogenomic test were given to clinicians

978
Usual care
Usual care and access to pharmacogenomic results after 24 weeks

OUTCOMES

Proportion of prescriptions with a predicted drug-gene interaction written in the 30 days after randomization and remission of depressive symptoms measured by the Patient Health Questionnaire-9

FINDINGS

Estimated risks of drug-gene interactions

Pharmacogenomic guided
None, **59.3%** | Moderate, **30.0%** | Substantial, **10.7%**

Usual care
None, **25.7%** | Moderate, **54.6%** | Substantial, **19.7%**

Estimated difference:
For none, **33.6%** (95% CI, 28.9% to 38.4%)
For moderate, **-24.6%** (95% CI, -29.5% to -19.7%)
For substantial, **-9.0%** (95% CI, -12.7% to -5.3%)

Higher symptom remission rates over 24 weeks for intervention vs usual care:
Odds ratio, **1.28** (95% CI, 1.05 to 1.57)
Risk difference, **2.8%** (95% CI, 0.6% to 5.1%)

OSLIN DW, ET AL.
JAMA. 2022;328(2):151-161

Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis

Giovanni Ostuzzi, Giovanni Vita, Federico Bertolini, Federico Tedeschi, Beatrice De Luca, Chiara Gastaldon, Michela Nosé, Davide Papola, Marianna Purgato, Cinzia Del Giovane, Christoph U Correll, Corrado Barbui**

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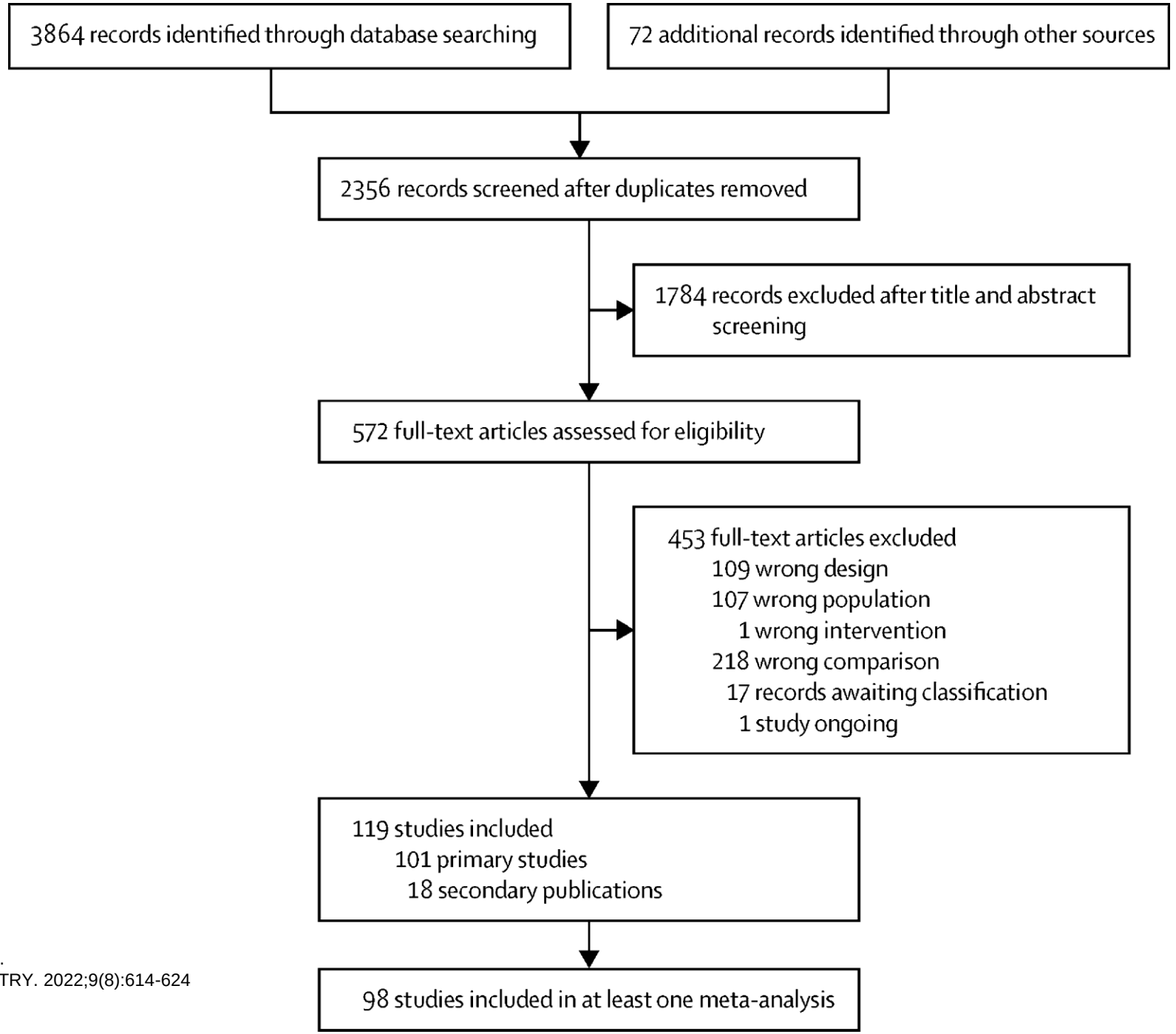
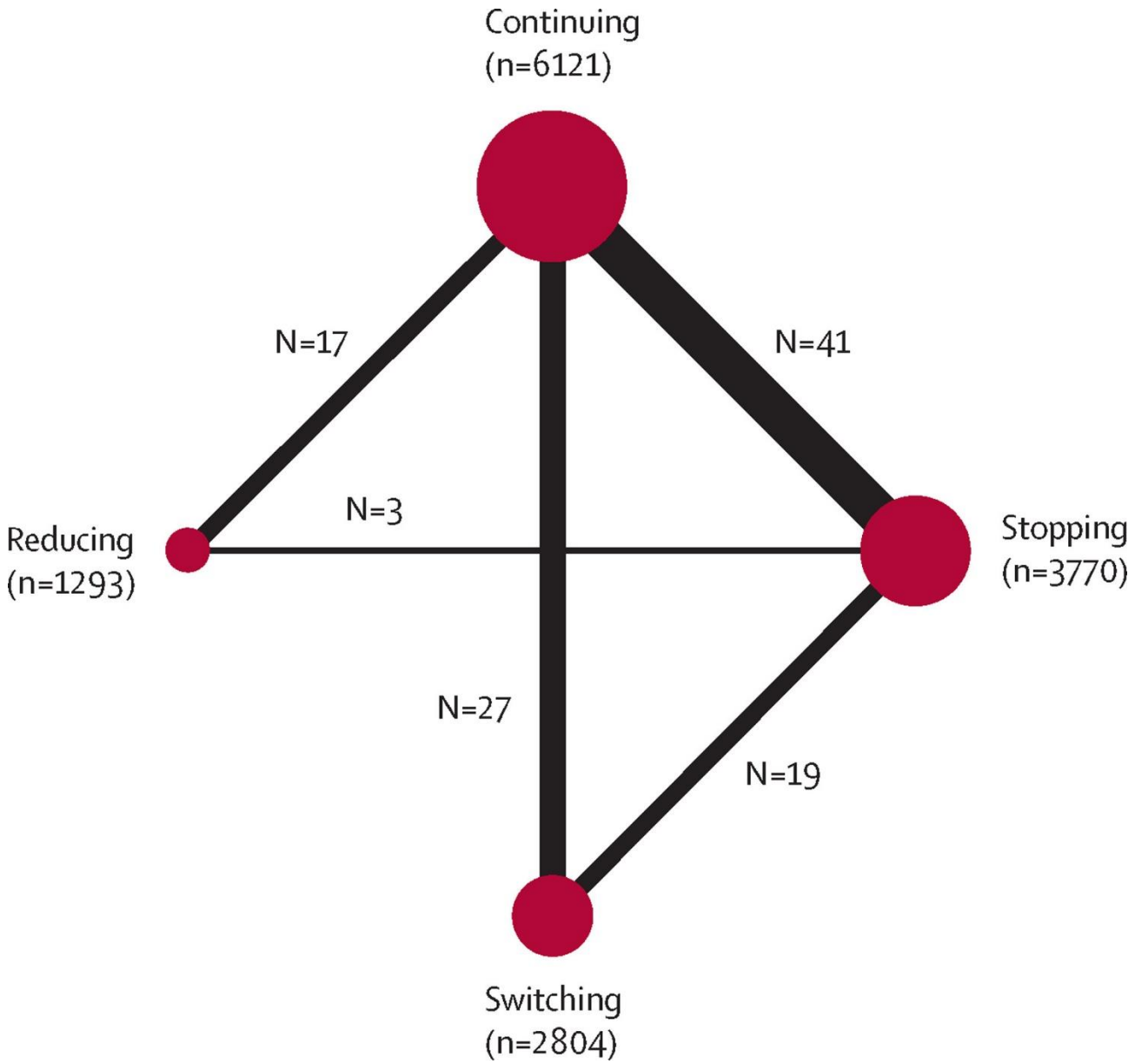

3864 records identified through database searching
72 additional records identified through other sources
2356 records screened after duplicates removed
1784 records excluded after title and abstract screening
572 full-text articles assessed for eligibility
453 full-text articles excluded
109 wrong design
107 wrong population
1 wrong intervention
218 wrong comparison
17 records awaiting classification
1 study ongoing
119 studies included
101 primary studies
18 secondary publications
98 studies included in at least one meta-analysis

	Relapse network
Number of studies	98
Number of individuals included	13 988
Sex, number of participants (%)	
Female	5315 (38·0%)
Male	8673 (62·0%)
Mean age (range), years	38·8 (23·2–63·9)
Diagnosis, percentage of studies	
Schizophrenia	72·5%
Schizoaffective disorder	1·0%
Schizophrenia and schizoaffective disorder	16·3%
Various schizophrenia-spectrum disorders	10·2%
Stage of disease, percentage of studies	
First episode	2·0%
Several episodes	94·9%
Unclear or mixed	3·1%
Mean duration of illness (range), years	12·1 (0·25–35·7)
Mean follow-up, percentage of studies	
6–24 weeks	40·8%
25–52 weeks	41·8%
≥53 weeks	17·4%
Study blinding, percentage of studies	
Double blind	79·6%
Open label	20·4%
Year of publication, percentage of studies	
Until 1989	52·0%
1990 to 2009	23·5%
2010 to 2019	24·5%
Setting, percentage of studies	
Inpatients	27·5%
Outpatients	53·1%
Mixed	19·4%

	Relapse network
(Continued from previous column)	
Country income, percentage of studies	
High and upper-middle income	89·8%
Lower-middle and low income	5·1%
Unclear or mixed	5·1%
Study design, percentage of studies	
Placebo controlled	62·2%
Active comparator only	37·8%
Antipsychotic treatment strategy, percentage of groups	
Continuing	40·6%
Reducing	9·6%
Switching	20·8%
Stopping (switch to placebo)	29·0%
Treatment formulation, percentage of groups	
Oral formulation	59·3%
LAI formulation	28·6%
Mixed formulations	12·1%
Antipsychotic class, percentage of groups	
First-generation antipsychotic	59·8%
Second-generation antipsychotic	34·2%
Mixed class of antipsychotics	6·0%

LAI=long-acting injectable antipsychotic.

Table 1: **Characteristics of randomised controlled trials included in the network meta-analysis for the primary outcome**



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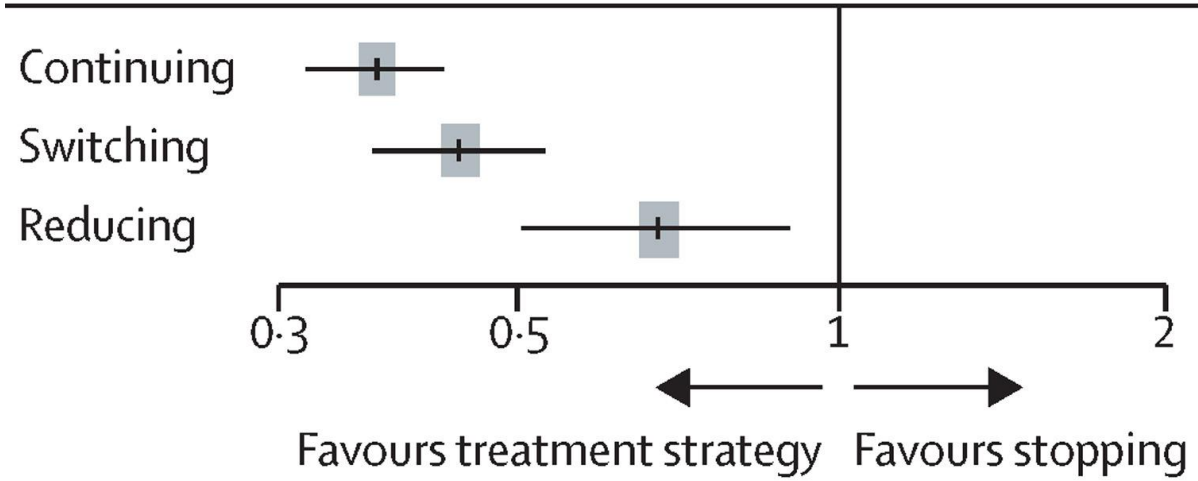
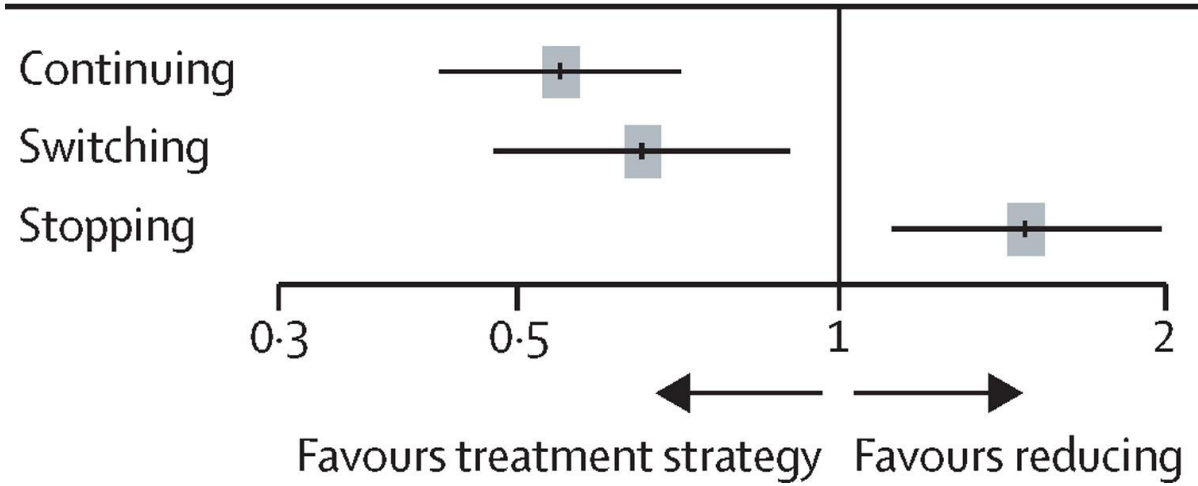
LANCET PSYCHIATRY. 2022;9(8):614-624

A Stopping as comparator



	RR (95% CI)	NNT (95% CI)	CINeMA
Continuing	0·37 (0·32–0·43)	NNTB 3·17 (2·94–3·51)	Moderate
Switching	0.44 (0·37–0·53)	NNTB 3·57 (3·17–4·25)	Moderate
Reducing	0·68 (0·51–0·90)	NNTB 6·25 (4·08–20·00)	Moderate

B Reducing as comparator



	RR (95% CI)	NNT (95% CI)	CINeMA
Continuing	0·55 (0·42–0·71)	NNTB 4·44 (3·45–6·90)	Moderate
Switching	0·65 (0·47–0·90)	NNTB 5·71 (3·77–18·18)	Moderate
Stopping	1·48 (1·11–1·97)	NNTH 4·17 (18·18–2·06)	Moderate

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	Relapse (effectiveness); N=98; n=13 988; RR (95% CI)	Mean change scores (efficacy); N=47; n=8878; SMD (95% CI)	Hospital admissions; N=29; n=5329; RR (95% CI)	Discontinuation due to inefficacy; N=44; n=9092; RR (95% CI)	Discontinuation due to any cause (acceptability); N=79; n=11 914; RR (95% CI)	Quality of life; N=8; n=1421; RR (95% CI)	Functional status; N=13; n=1998; RR (95% CI)	Discontinuation due to adverse events (tolerability); N=48; n=9798; RR (95% CI)
Continuing *vs* stopping	0·37 (0·32 to 0·43)	−0·78 (−0·99 to −0·57)	0·53 (0·41 to 0·67)	0·38 (0·31 to 0·47)	0·81 (0·69 to 0·95)	0·50 (0·15 to 0·85)	0·55 (0·20 to 0·90)	1·09 (0·77 to 1·54)
Reducing *vs* stopping	0·68 (0·51 to 0·90)	−0·67 (−1·06 to −0·29)	0·62 (0·38 to 1·01)	0·89 (0·56 to 1·43)	0·86 (0·64 to 1·16)	0·40 (−0·26 to 1·06)	0·79 (0·07 to 1·50)	1·55 (0·79 to 3·02)
Switching *vs* stopping	0·44 (0·37 to 0·53)	−0·70 (−0·95 to −0·45)	0·56 (0·38 to 0·83)	0·49 (0·39 to 0·61)	0·84 (0·70 to 1·01)	0·47 (−0·06 to 1·01)	0·53 (−0·11 to 1·18)	1·26 (0·87 to 1·84)
Continuing *vs* reducing	0·55 (0·42 to 0·71)	−0·10 (−0·43 to 0·22)	0·85 (0·53 to 1·37)	0·42 (0·28 to 0·65)	0·94 (0·73 to 1·22)	0·10 (−0·46 to 0·66)	−0·24 (−0·86 to 0·39)	0·70 (0·40 to 1·24)
Continuing *vs* switching	0·84 (0·69 to 1·02)	−0·08 (−0·30 to 0·15)	0·94 (0·66 to 1·35)	0·78 (0·58 to 1·04)	0·97 (0·81 to 1·16)	0·03 (−0·37 to 0·42)	0·02 (−0·61 to 0·64)	0·86 (0·56 to 1·32)
Reducing *vs* switching	1·53 (1·12 to 2·11)	0·03 (−0·37 to 0·42)	1·11 (0·62 to 1·99)	1·84 (1·10 to 3·08)	1·03 (0·75 to 1·40)	−0·08 (−0·76 to 0·61)	0·25 (−0·63 to 1·14)	1·22 (0·60 to 2·50)

RRs and 95% CIs are reported. RRs lower than 1 favour the first treatment strategy reported. For mean change scores (efficacy), SMDs and 95% CIs are reported. SMDs lower than 0 favour the first treatment strategy reported. N=number of studies included. n=number of participants included. RR=relative risk. SMD=standardised mean differences.

Table 2: **Results of the network meta-analysis comparing treatment strategies for each outcome**

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Research in context

Evidence before this study

Schizophrenia is a severely disabling, usually chronic condition. Antipsychotic maintenance treatment is widely recommended by clinical guidelines, and generally it consists in continuing the antipsychotic that provided benefit in the acute phase. However, burdensome long-term adverse events might threaten adherence and require a different treatment strategy, including switching to another antipsychotic, reducing the dose, or even stopping the antipsychotic. Evidence on the differential effectiveness of these strategies is scarce. We searched PubMed from inception up to Jan 11, 2021, for the following search terms in the title and abstract: ((schizophreni* OR schizoaffective OR delusional OR psychotic) AND (stabil* OR chronic* OR long-term OR maintenance) AND (antipsychotic*) AND (continu* OR stay OR switch* OR reduc* OR lower* OR stop* OR discontinu* OR withdraw*) AND meta-analysis), without language restrictions. Among 88 records, we did not find network meta-analyses comparing the four maintenance treatment strategies. Among pairwise meta-analyses of randomised controlled trials, two compared standard and reduced antipsychotic doses, one compared antipsychotic discontinuation and maintenance in first-episode remitted individuals, and four investigated various strategies for managing long-term adverse events.

Added value of this study

To our knowledge, this network meta-analysis is the first to compare the risk of relapse of three different maintenance treatment strategies and antipsychotic discontinuation in individuals with schizophrenia. Compared to stopping the antipsychotic, all maintenance strategies were effective in preventing relapse. We found continuing at standard doses and switching to a different antipsychotic to be similarly effective, despite previous evidence suggesting switching to be associated with higher risk. Both these maintenance strategies significantly outperformed antipsychotic dose reduction below standard doses.

Implications of all the available evidence

Our findings support updating clinical guidelines to recognise that switching to another antipsychotic during maintenance treatment can be as effective as continuing antipsychotics at standard dose, whereas dose reduction below standard doses should be limited to selected cases.

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