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Intranasal antihistamines and corticosteroids in the treatment of allergic rhinitis: A systematic review and meta-analysis protocol

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Amendments: This protocol does not represent an amendment of a previously completed or published protocol. Eventual important protocol amendments will be reported in the systematic review.

Abstract

Introduction: Intranasal antihistamines and corticosteroids are some of the most frequently used drug classes in the treatment of allergic rhinitis. However, there is uncertainty as to whether effectiveness differences may exist among different intranasal specific medications. This systematic review aims to analyse and synthesise all evidence from randomised controlled trials (RCTs) on the effectiveness of intranasal antihistamines and corticosteroids in rhinitis nasal and ocular symptoms and in rhinoconjunctivitis-related quality-of-life.

Methods and analysis: We will search four electronic bibliographic databases and three clinical trials databases for RCTs (i) assessing adult patients with seasonal or perennial allergic rhinitis and (ii) comparing the use of intranasal antihistamines or corticosteroids *versus* placebo. Assessed outcomes will include the Total Nasal Symptom Score (TNSS), the Total Ocular Symptom Score (TOSS) and the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ). We will assess the methodological quality of included primary studies by using the Cochrane risk-of-bias tool. Certainty in the body of evidence for the analysed outcomes will be assessed using the GRADE approach. We will perform a random-effects meta-analysis for each assessed medication and outcome, presenting results as pooled mean differences and standardised mean differences. Heterogeneity will be explored by sensitivity and subgroup analyses, considering the risk of bias, follow-up period and drug dose of the primary studies.

Ethics and dissemination: Ethical considerations will not be required. Results will be disseminated in a peer-review journal.

Strengths and limitations of this study:

- We will analyse evidence from randomised controlled trials assessing intranasal antihistamines and corticosteroids, two of the most frequently used drug classes in the treatment of allergic rhinitis.
- We will perform meta-analysis on three relevant outcomes, exploring sources of heterogeneity based on the risk of bias, follow-up period or doses of the drugs (among others).
- There will be some limitations stemming from the fact that (i) only trials assessing adults and (ii) only comparisons against placebo will be considered.

Introduction

Allergic rhinitis is a common chronic condition with a prevalence of up to 50% in some countries[1]. While not being potentially fatal, allergic rhinitis has a relevant impact on work and school productivity, as well as on patients' quality of life[2-4]. Pharmacological interventions for allergic rhinitis have evolved over the last decades, with the current mainstay treatment including oral or intranasal antihistamines, intranasal steroids and fixed combinations of intranasal steroids + antihistamines. In this context, the 2020 Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines preferentially favour the use of intranasal medication, considering that (i) intranasal steroids or fixed combinations of intranasal steroids + antihistamines display higher effectiveness than oral or intranasal antihistamines and (ii) intranasal treatments display a faster onset of action than oral ones[5]. However, for most recommendations, the level of evidence was reported to be "low" or "very low"[5]. In addition, there is insufficient evidence as to whether effectiveness differences may exist among different intranasal specific medications. This prompts the need for a systematic assessment – using a standardised approach – on the effectiveness of each specific intranasal antihistamine or steroid. This is even more relevant given not only a large amount of evidence unpublished in scientific journals but also the fact that randomised controlled trials (RCTs) assessing the effectiveness of intranasal rhinitis medications are quite heterogeneous on their methodological quality and methods for outcome assessment (e.g., scores used to quantify nasal or ocular symptoms).

Therefore, the main aim of this systematic review will be to analyse and synthesise all evidence from randomised controlled trials (RCT) on the efficacy of intranasal antihistamines and intranasal steroids in rhinitis nasal and ocular symptoms and in rhinoconjunctivitis-related quality-of-life. The obtained results will allow us not only to acquire pooled meta-analytical estimates on the efficacy of each specific drug, but also to assess the certainty in the existing body of evidence.

Methods and analyses

We will perform a systematic review of RCTs assessing the efficacy of intranasal antihistamines and/or corticosteroids in the treatment of patients with allergic rhinitis. This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6].

Eligibility criteria

We will include RCTs assessing patients ≥12 years old with seasonal or perennial allergic rhinitis and comparing the use of intranasal antihistamines or corticosteroids or their combination *versus* placebo (direct comparisons between active drugs will not be considered) on at least one of the following patient-reported outcome measures (selected as they correspond to the most common efficacy outcomes assessed in rhinitis trials, providing information on different disease domains): Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), Total Symptom Score (TSS), or

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). We define the TNSS as any score computed based on the sum of several patient-reported scores for individual nasal symptoms. Accordingly, we define the TOSS as any score computed based on the sum of several patient-reported scores for individual ocular symptoms, while the TSS implies the combination of different types of rhinitis symptoms (e.g., nasal, ocular and/or palate symptoms). The TNSS, TOSS and TSS will be assessed in a reflective manner; that is, as reflecting the patient's symptoms in the previous 12 or 24 hours. The following intranasal drugs will be considered: azelastine, azelastine-fluticasone, beclomethasone, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, levocabastine, mometasone furoate, olopatadine, olopatadine-mometasone and triamcinolone. We will only include RCTs with a parallel design, given the difficulties associated with cross-over studies associated with the duration of the pollen season (for seasonal allergic rhinitis) and with symptom attenuation (for perennial allergic rhinitis). In addition, considering Food and Drug Administration recommendations[7], we will only include studies with a follow-up period of at least two weeks if assessing patients with seasonal allergic rhinitis or at least four weeks if assessing patients with perennial allergic rhinitis.

We will exclude RCTs assessing patients with seasonal allergic rhinitis that are not conducted during the pollen season or in which treatment started before the beginning of the pollen season. No exclusion criteria will be applied based on the publication language, date or status.

Information sources and search strategy

We will search MEDLINE (via Ovid), Web of Science, Embase and CENTRAL (Cochrane Central Register of Controlled Trials) from database inception. In addition, we will manually search the clinicaltrials.gov, the GSK clinical study dataset and the AstraZeneca Clinical Trials Website in order to identify potentially unpublished trials. Search queries to be applied are listed in the Supplementary Table 1.

Study selection and data collection

After duplicates removal, each record will be independently assessed by two authors, first by title and abstract screening and subsequently by full-text reading. For each included record, we will assess whether additional publications from the same study are available (in order to avoid duplication of information from the same participants). Two reviewers will independently extract data from each included primary study using a purpose-built online form (a pilot version of the form will be initially developed, with the definitive version being made available after the assessment of the first three RCTs). From each study, we will retrieve information on (i) the assessed disease (seasonal *versus* perennial allergic rhinitis), (ii) the participants' inclusion and exclusion criteria (as stated in the each study's description), (iii) the data collection period, (iv) the places from where patients were recruited, (v) the active treatment daily dose, (vi) the follow-up period, (vii) the number of randomised participants (as

well as their age and gender distribution) and (viii) the number of participants completing the trial (despite that, for each outcome, we will assess the effects among all patients who had the outcome measured). We will also extract the information required to assess the risk of bias in each study. In addition, for each reported outcome (TNSS, TOSS, TSS and/or RQLQ), we will retrieve information on the scale and computation method, baseline values and post-intervention and/or change from baseline values, when available. If results are only provided in graphs, estimates will be obtained using the PlotDigitizer tool (https://plotdigitizer.com/).

Disagreements between reviewers in data selection or extraction will be solved by consensus or by a third reviewer. Authors of included primary studies will be contacted to provide missing information.

Risk of bias and certainty assessment

The risk of bias of each included primary study will be independently assessed by two researchers using the Cochrane Risk of Bias tool. For the "blinding of outcome assessment" and "incomplete outcome data" items, assessments will be separately performed for each reported outcome. The risk of selective reporting will be assessed not only by reading the study's methods, but also by analysing the trial protocol or registration if available. Disagreements between reviewers will be solved by consensus or by a third reviewer.

Certainty in the body of evidence for each outcome and across outcomes will be assessed using the GRADE approach[8]. In order to assess whether a strong association is obtained, we will analyse not only whether the meta-analytical point estimate for each outcome is higher than the minimal important difference, but also whether such value is not contained in the respective confidence interval. For RQLQ, on a 0-6 scale, we will consider a minimal important difference of 0.5[9]. For the TNSS, on a 0-12 scale, we will consider a minimal important difference of 0.28 (following the work of Barnes et al.[10]).

Quantitative synthesis of results

All assessed outcomes are continuous. Therefore, for each group in each primary study, we will present the mean (± standard-deviation) baseline and change-from-baseline value for all outcomes of interest. Any missing information on spread measures (standard-deviation, standard-error or variance) will be estimated using the algorithm suggested by Weir et al.[11] (itself an adaptation of that proposed by Weibe et al.[12]) and in accordance with Cochrane recommendations[13]. In summary, we will attempt to apply one of the following methods in the following hierarchical order: (i) use of algebraic recalculation to recover missing data, (ii) contacting of study authors to retrieve missing data, (iii) use of approximate algebraic calculations based on other study-level measures (e.g., range or quartiles), (iv) use of multiple imputation methods, (v) use of non-parametric summaries, (vi) use of single-imputation methods, (vii) summary of non-pooled data alongside meta-analysed results in the systematic review text (Figure 1).

As recommended by the Cochrane handbook, (i) obtention of missing data based on the methods iii-vii will only occur if missing data occurs in a small proportion of studies, and (ii) sensitivity analyses will always be performed to assess the impact of dealing with missing data[13].

We will perform random-effects meta-analyses of mean differences (MD; if scores are measured using the same scale) or standardised-mean differences (SMD; if scores are measured using different scales) in change-from-baseline values (active treatment *versus* placebo). For outcomes calculated based on the same symptoms and giving the same weight to each symptom but with results presented in different scales (e.g., two studies calculating the TNSS based on the same symptoms, but with one presenting the results on a scale of 0-12 and another on a scale 0-24), scales will be reconverted into a scale of 0-12 for the TNSS and of 0-9 for the TOSS. Separate meta-analyses will be performed for patients with seasonal and perennial allergic rhinitis.

The restricted maximum likelihood approach will be used to estimate between-study variance. Heterogeneity will be assessed by estimating the *p*-value of the Q-Cochran test and by the I^2 statistic. Irrespective of the amount of detected heterogeneity, sensitivity analyses will be performed excluding studies (i) with high risk of bias, and (ii) in which algebraic calculations needed to be performed to estimate missing data, (iii) based on the follow-up period of the study, and (iv) based on the doses of the drugs being assessed. In the presence of substantial heterogeneity, leave-one-out sensitivity analyses will also be performed.

All analyses will be performed using software R, with the use of the metafor and meta packages.

Patient and Public Involvement statement

There will be no Patient or Public Involvement in this study.

Ethics and dissemination

Ethical considerations will not be required. Results will be disseminated in a peer-review journal. Data can be made available from the corresponding author upon reasonable request.

Discussion

This systematic review and meta-analysis will be a first step to assess the efficacy of specific intranasal antihistamines and corticosteroids in the treatment of allergic rhinitis. While there will be some limitations in terms of generalisability (e.g., as only RCTs with adults will be included) or related to the fact that only comparisons against placebo will be considered, these limitations may be overcome by future complementary studies (e.g., a systematic review of RCTs in paediatric patients or a network meta-analysis on intranasal treatments for allergic rhinitis).

Our study will synthesise data from RCTs to determine the impact of intranasal antihistamines and corticosteroids on nasal symptoms, ocular symptoms and quality of life of patients with allergic rhinitis. In addition, it will enable us to assess the methodological quality and certainty in the body of existing evidence, allowing us to make robust conclusions on the efficacy of these treatments. The findings of this systematic review may support recommendations in future guidelines on allergic rhinitis treatment, as well as lay the basis for a future network meta-analysis, taking into account both direct and indirect comparisons between specific drugs.

Authors' contributions: BSP, RJV, JAF and JB participated in the study design and in the drafting of the protocol manuscript. JB, ACF, NLS, RFS, AF, SGM, AB, LK, TZ and HJS participated in the study design and in the critical revision of the manuscript. JB is the guarantor of the review.

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Competing interest statement:

L. Klimek reports grants from Allergopharma, MEDA/Mylan, ALK Abelló, LETI Pharma, Stallergenes, Sanofi, ASIT biotech, Lofarma Quintiles, AstraZeneca, GSK, and Inmunotk; and personal fees from Allergopharma, MEDA/Mylan, HAL Allergie, LETI Pharma, Sanofi, Allergy Therapeut, and Cassella Med, outside the submitted work.

J. A Fonseca reports grants from Astrazeneca and Mundipharma; and personal fees from AstraZeneca, Mundipharma, Sanofi, GSK, and Teva, outside the submitted work.

T. Zuberbier reports grants from Novartis and Henkel; personal fees from Bayer Health Care, FAES, Novartis, Henkel, AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bencard, Berlin Chemie, HAL, Leti, Meda, Menarini, Merck, MSD, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, Kryolan, and L'Oréal, outside the submitted work.

J. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, and Uriach; and other from Kyomed-Innov, outside the submitted work.

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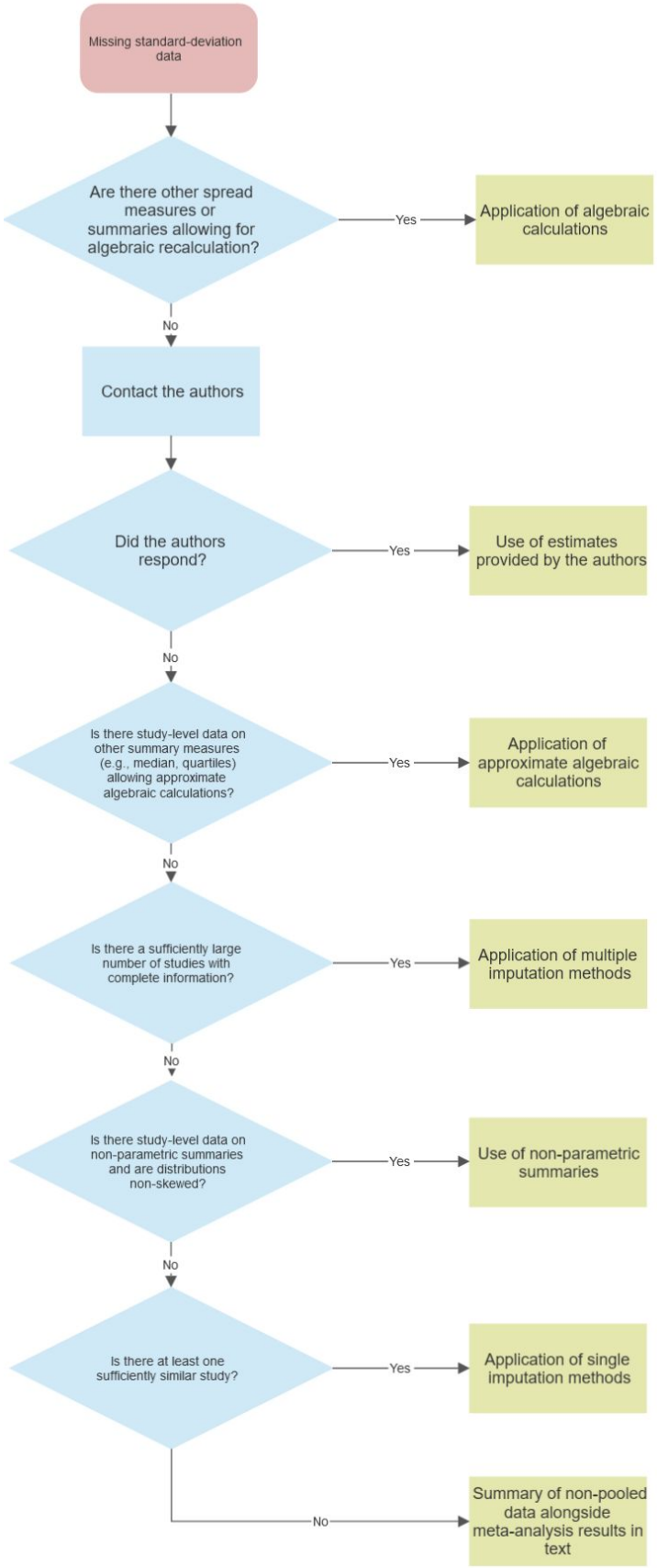
Figure 1. Approach that will be followed to estimate missing standard-deviation data from included primary studies



Supplementary Material

Supplementary Table 1. Queries applied in the different bibliographic databases

MEDLINE (Ovid)	
1	azelastin$.mp.
2	azelastine-fluticasone.mp.
3	azeflu.mp.
4	MP-azeflu.mp.
5	(azelastine adj2 fluticasone).mp.
6	dymista.mp.
7	azecort.mp.
8	olopatadin$.mp.
9	olopatadine-mometasone.mp.
10	(olopatadine adj2 mometasone).mp.
11	gsp301.mp.
12	ryaltris.mp.
13	levocabastin$.mp.
14	lexicomp.mp.
15	ciclesonid$.mp.
16	Alvesco.mp.
17	fluticason$.mp.
18	GW685698X.mp.
19	mometason$.mp.
20	beclometason$.mp.
21	budesonid$.mp.
22	triamcinolon$.mp.
23	azelastine.nm.
24	levocabastine.nm.
25	ciclesonide.nm.
26	exp Olopatadine Hydrochloride/
27	exp Fluticasone/
28	exp Mometasone Furoate/
29	exp Beclomethasone/
30	exp Budesonide/
31	exp Triamcinolone/
32	exp Rhinitis/

33 (rhinit$ or rhinoconjunctivit$).mp.
34 exp Allergic Rhinitis/
35 (hayfever or "hay fever" or pollenosis or pollinosis or SAR).mp.
36 (spray or aerosol or powder or inhal$ or solution or turbuhaler or intranasal$ or (intra adj1 nasal) or topical$ or nose or nostril$).mp.
37 exp Administration, Topical/
38 exp Administration, Intranasal/
39 or/1-31
40 or/32-35
41 or/36-38
42 39 and 40 and 41
43 randomized controlled trial.pt.
44 controlled clinical trial.pt.
45 randomized.ab.
46 placebo.ab.
47 clinical trials as topic.sh.
48 randomly.ab.
49 trial.ti.
50 43 or 44 or 45 or 46 or 47 or 48 or 49
51 exp animals/ not humans.sh.
52 50 not 51
53 42 and 52

CENTRAL (CRS Web)

1 (azelastin*):ti,ab,kw OR (azelastine-fluticasone):ti, ab,kw OR (azeflu):ti,ab,kw OR (mp-azeflu):ti, ab,kw OR (azelastine AND fluticasone):ti,ab,kw
2 (dymista):ti,ab,kw OR (azecort):ti, ab,kw OR (olopatadin*):ti,ab, kw OR (olopatadine-mometasone):ti, ab, kw OR ((olopatadine AND mometasone)):ti,ab,kw
3 (gsp301):ti,ab,kw OR (ryaltris):ti,ab,kw OR (levocabastin*):ti,ab,kw OR (lexicomp):ti, ab, kw OR (ciclesonid*):ti,ab,kw
4 (alvesco):ti,ab,kw OR (fluticason*):ti,ab, kw OR (gw685698x):ti, ab, kw OR (mometason*):ti, ab, kw OR (beclometason*):ti,ab,kw
5 (budesonid*):ti,ab,kw OR (triamcinolon*):ti, ab,kw
6 MESH DESCRIPTOR: [Olopatadine Hydrochloride] EXPLODE ALL
7 MESH DESCRIPTOR: [Fluticasone] EXPLODE ALL
8 MESH DESCRIPTOR: [Mometasone Furoate] EXPLODE ALL
9 MESH DESCRIPTOR: [Beclomethasone] EXPLODE ALL

10	MESH DESCRIPTOR: [Budesonide] EXPLODE ALL
11	MESH DESCRIPTOR: [Triamcinolone] EXPLODE ALL
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	MESH DESCRIPTOR: [Rhinitis] EXPLODE ALL
14	(rhinit*):ti,ab,kw OR (rhinoconjunctivit*):ti, ab,kw
15	MESH DESCRIPTOR: [Rhinitis, Allergic] EXPLODE ALL
16	(hayfever):ti,ab, kw OR ("hay fever"):ti, ab, kw OR (pollenosis):ti,ab,kw OR (pollinosis):ti, ab, kw OR ("SAR"):ti,ab,kw
17	#13 OR #14 OR # 15 OR #16
18	(spray*):ti,ab,kw OR (aerosol):ti, ab, kw OR (powder):ti,ab,kw OR (inhal*):ti,ab, kw OR (solution):ti,ab,kw
19	(turbuhaler):ti, ab,kw OR (intranasal*):ti,ab,kw OR (nasal):ti, ab,kw OR (topical*):ti, ab,kw OR (nose):ti, ab,kw
20	(nostril*):ti,ab,kw
21	MESH DESCRIPTOR: [Administration, Topical] EXPLODE ALL
22	MESH DESCRIPTOR: [Administration, Intranasal] EXPLODE ALL
23	#18 OR #19 OR #20 OR #21 OR #22
24	#12 AND #17 AND #23

Embase

1	(azelastin$ or azelastine-fluticasone or azeflu or MP-azeflu or (azelastine adj2 fluticasone) or dymista or azecort or olopatadin$ or olopatadine-mometasone or (olopatadine adj2 mometasone) or gsp301 orryaltris or levocabastin$ or lexicomp or ciclesonid$ or Alvesco or fluticason$ or GW685698X or mometason$ or beclometason$ or budesonid$ or triamcinolon$).tw.
2	(rhinit$ or rhinoconjunctivit$ or hayfever or "hay fever" or pollenosis or pollinosis).tw.
3	(((spray$ or aerosol or powder or inhal$ or solution or turbuhaler or intranasal$).tw. or intra.mp.) adj1 nasal.tw.) or topical$.tw. or nose.tw. or nostril$.tw. or nasal.tw.
4	1 and 2 and 3
5	randomized controlled trial/
6	controlled clinical study/
7	5 or 6
8	random$.ti,ab.
9	randomization/
10	intermethod comparison/
11	placebo.ti,ab
12	(compare or compared or comparison).ti.

13 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
14 (open adj label).ti,ab.
15 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
16 double blind procedure/
17 parallel group$1.ti,ab.
18 (crossover or cross over).ti, ab.
19 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
20 (assigned or allocated).ti,ab.
21 (controlled adj7 (study or design or trial)).ti,ab.
22 (volunteer or volunteers).ti,ab.
23 human experiment/
24 trial.ti.
25 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 25 not 7
27 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
28 (Systematic review not (trial or study)).ti.
29 (nonrandom$ not random$).ti, ab.
30 "Random field$"ti,ab.
31 (random cluster adj3 sampl$).ti,ab.
32 (review.ab. and review.pt.) not trial.ti.
33 "we searched".ab. and (review.ti. or review.pt.)
34 "update review".ab.
35 (databases adj4 searched).ab.
36 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
37 37 Animal experiment/not (human experiment/or human/)
38 or/27-37
39 26 not 38
40 4 and 39

Web of Science

1 TS=(azelastin* OR azelastine-fluticasone OR azeflu OR MP-azeflu OR (azelastine NEAR/2 fluticasone) OR dymista OR azecort OR olopatadin* OR olopatadine-mometasone OR (olopatadine NEAR/2 mometasone) OR gsp301 OR ryaltris OR levocabastin* OR lexicomp OR ciclesonid* OR Alvesco OR fluticason* OR GW685698X OR mometason* OR beclometason* OR budesonid* OR triamcinolon*)

2 TS=(rhinit* or rhinoconjunctivit*) OR TS=(hayfever or "hay fever" or pollenosis or pollinosis or SAR)

3 TS=(spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or (intra NEAR/1 nasal) or topical* or nose or nostril*)

4 TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))

5 TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa

or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider

	monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes)
6	#4 NOT #5
7	#1 AND #2 AND #3 AND #6

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review - Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such - Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author - Pages 1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review - Page 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments - Page 2
Support:		
Sources	5a	Indicate sources of financial or other support for the review - Page 8
Sponsor	5b	Provide name for the review funder and/or sponsor - Page 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol - Page 8
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known - Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) - Page 4
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Supplementary Table 1
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 5

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 5-6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Page 5-6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Pages 4-5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis - Page 6; Page 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised - Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) - Page 6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) - Page 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned - Not applicable. Quantitative synthesis appropriate
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) - Page 6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) - Page 6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Intranasal antihistamines and corticosteroids in the treatment of allergic rhinitis: A systematic review and meta-analysis protocol

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Intranasal antihistamines and corticosteroids in the treatment of allergic rhinitis: A systematic review and meta-analysis protocol

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Amendments: This protocol does not represent an amendment of a previously completed or published protocol. Eventual important protocol amendments will be reported in the systematic review.

Abstract

Introduction: Intranasal antihistamines and corticosteroids are some of the most frequently used drug classes in the treatment of allergic rhinitis. However, there is uncertainty as to whether effectiveness differences may exist among different intranasal specific medications. This systematic review aims to analyse and synthesise all evidence from randomised controlled trials (RCTs) on the effectiveness of intranasal antihistamines and corticosteroids in rhinitis nasal and ocular symptoms and in rhinoconjunctivitis-related quality-of-life.

Methods and analysis: We will search four electronic bibliographic databases and three clinical trials databases for RCTs (i) assessing patients ≥12 years old with seasonal or perennial allergic rhinitis and (ii) comparing the use of intranasal antihistamines or corticosteroids *versus* placebo. Assessed outcomes will include the Total Nasal Symptom Score (TNSS), the Total Ocular Symptom Score (TOSS) and the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ). We will assess the methodological quality of included primary studies by using the Cochrane risk-of-bias tool. Certainty in the body of evidence for the analysed outcomes will be assessed using the GRADE approach. We will perform a random-effects meta-analysis for each assessed medication and outcome, presenting results as pooled mean differences and standardised mean differences. Heterogeneity will be explored by sensitivity and subgroup analyses, considering (i) the risk of bias, (ii) the follow-up period and (iii) the drug dose.

Ethics and dissemination: Ethical considerations will not be required. Results will be disseminated in a peer-review journal.

PROSPERO registration number: CRD42023416573.

Strengths and limitations of this study:

- We will analyse evidence by searching four electronic bibliographic databases and complementing the search with a manual search in three trial databases.
- There will be no language- or publication date-based exclusion criteria.
- We will perform meta-analyses on three relevant outcomes, exploring sources of heterogeneity based on the risk of bias, follow-up period or doses of the drugs.
- We will only include trials assessing patients ≥12 years old and, therefore, our results may not be generalisable to children.
- We will only consider comparisons against placebo.

Introduction

Allergic rhinitis is a common chronic condition with a prevalence of up to 50% in some countries.[1] While not being potentially fatal, allergic rhinitis has a relevant impact on work and school productivity, as well as on patients' quality of life.[2-4] Pharmacological interventions for allergic rhinitis have evolved over the past decades, with the current mainstay treatment including oral or intranasal antihistamines, intranasal corticosteroids and fixed combinations of intranasal corticosteroids + antihistamines. In this context, the 2020 Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines preferentially favour the use of intranasal medication, considering that (i) intranasal corticosteroids or fixed combinations of intranasal corticosteroids + antihistamines display higher effectiveness than oral or intranasal antihistamines and (ii) intranasal treatments display a faster onset of action than oral treatments.[5] However, for most recommendations, the level of evidence was reported to be "low" or "very low".[5] In addition, there is insufficient systematised evidence on the quantitative effectiveness of each specific intranasal medication. While there have been other systematic reviews assessing intranasal medications for allergic rhinitis, they either (i) focused on a single medication,[6, 7] (ii) did not specifically provide data for each medication within the same class,[8, 9] or (iii) displayed a different aim (e.g., Juel-Berg et al. sought to compare intranasal corticosteroids *versus* oral antihistamines).[8]. This prompts the need for a systematic assessment – using a standardised approach – on the effectiveness of each specific intranasal antihistamine or steroid. This is even more relevant given not only the large amount of evidence unpublished in scientific journals but also the fact that randomised controlled trials (RCTs) assessing the effectiveness of intranasal rhinitis medications are quite heterogeneous on their methodological quality and methods for outcome assessment (e.g., scores used to quantify nasal or ocular symptoms).

Therefore, the main aim of this systematic review will be to analyse and synthesise all evidence from randomised controlled trials (RCTs) on the efficacy of intranasal antihistamines and intranasal corticosteroids in rhinitis nasal and ocular symptoms and in rhinoconjunctivitis-related quality-of-life. The obtained results will allow us not only to acquire pooled meta-analytical estimates on the efficacy of each specific drug, but also to assess the certainty in the existing body of evidence.

Methods and analyses

We will perform a systematic review of RCTs assessing the efficacy of intranasal antihistamines and/or corticosteroids in the treatment of patients with allergic rhinitis. This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10]

Eligibility criteria

We will include RCTs assessing patients ≥12 years old with seasonal or perennial allergic rhinitis and comparing the use of intranasal antihistamines or corticosteroids or their combination *versus* placebo

(direct comparisons between active drugs will not be considered) on at least one of the following patient-reported outcome measures (selected as they correspond to the most common efficacy outcomes assessed in rhinitis trials, providing information on different disease domains): Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), Total Symptom Score (TSS), or Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). We define the TNSS as any score computed based on the sum of several patient-reported scores for individual nasal symptoms. Accordingly, we define the TOSS as any score computed based on the sum of several patient-reported scores for individual ocular symptoms, while the TSS implies the combination of different types of rhinitis symptoms (e.g., nasal, ocular and/or palate symptoms). The TNSS, TOSS and TSS will be assessed in a reflective manner; that is, reflecting the patient's symptoms in the previous 12 or 24 hours. The following intranasal drugs will be considered: azelastine, azelastine-fluticasone, beclomethasone, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, levocabastine, mometasone furoate, olopatadine, olopatadine-mometasone and triamcinolone. We will only include RCTs with a parallel design, given the difficulties related to cross-over studies associated with the duration of the pollen season (for seasonal allergic rhinitis) and with symptom attenuation (for perennial allergic rhinitis). In addition, considering Food and Drug Administration recommendations,[11] we will only include studies with a follow-up period of (i) at least two weeks, if assessing patients with seasonal allergic rhinitis or (ii) at least four weeks, if assessing those with perennial allergic rhinitis.

We will exclude RCTs assessing patients with seasonal allergic rhinitis that are not conducted during the pollen season or in which treatment started before the beginning of the pollen season. No exclusion criteria will be applied based on the publication language, date or status.

Information sources and search strategy

We will search MEDLINE (via Ovid), Web of Science, Embase and CENTRAL (Cochrane Central Register of Controlled Trials) from database inception up to August 2022 (with a search update being performed in September 2023). In addition, we will manually search the clinicaltrials.gov, the GSK clinical study dataset and the AstraZeneca Clinical Trials Website in order to identify potentially unpublished trials. Search queries to be applied are listed in the Supplementary Table 1.

Study selection and data collection

After duplicates removal, each record will be independently assessed by two authors, first by title and abstract screening and subsequently by full-text reading. For each included record, we will assess whether additional publications from the same study are available (in order to avoid duplication of information from the same participants). Two reviewers will independently extract data from each included primary study using a purpose-built online form (a pilot version of the form will be initially developed, with the definitive version being made available after the assessment of the first three RCTs).

From each study, we will retrieve information on (i) the assessed disease (seasonal *versus* perennial allergic rhinitis), (ii) the participants' inclusion and exclusion criteria (as stated in each study description), (iii) the data collection period, (iv) the places where patients were recruited, (v) the active treatment daily dose, (vi) the follow-up period, (vii) the number of randomised participants (as well as their age and gender distribution) and (viii) the number of participants completing the trial (despite the fact that, for each outcome, we will assess the effects among all patients who had the outcome measured). We will also extract the information required to assess the risk of bias in each study. In addition, for each reported outcome (TNSS, TOSS, TSS and/or RQLQ), we will retrieve information on the scale and computation method, baseline values and post-intervention and/or change from baseline values, when available. If results are only provided in graphs, estimates will be obtained using the PlotDigitizer tool (https://plotdigitizer.com/).

Disagreements between reviewers in data selection or extraction will be solved by consensus or by a third reviewer. Authors of the included primary studies will be contacted to provide missing information.

Risk of bias and certainty assessment

The risk of bias of each included primary study will be independently assessed by two researchers using the Cochrane Risk of Bias tool. For the "blinding of outcome assessment" and "incomplete outcome data" items, assessments will be performed separately for each reported outcome. The risk of selective reporting will be assessed not only by reading the study's methods, but also by analysing the trial protocol or registration if available. Disagreements between reviewers will be solved by consensus or by a third reviewer.

Certainty in the body of evidence for each outcome and across outcomes will be assessed using the GRADE approach.[12] In order to assess whether a strong association is obtained, we will verify if (i) the meta-analytical point estimate for each outcome is higher than the minimal important difference, and also (ii) if this value is not contained in the respective confidence interval. For RQLQ, on a 0-6 scale, we will consider a minimal important difference of 0.5.[13] For the TNSS, on a 0-12 scale, we will consider a minimal important difference of 0.28 (following the work of Barnes et al.[14]). For the assessment of the possibility of publication biases, we will consider whether (i) small and large studies converge on the same effect estimates, (ii) there has been an earlier publication of positive results and (iii) there is information on registered RCTs without published results.

Quantitative synthesis of results

All assessed outcomes are continuous. Therefore, for each group in each primary study, we will present the mean (± standard-deviation) baseline and change-from-baseline value for all outcomes of interest. Any missing information on spread measures (standard-deviation, standard-error or variance) will be

estimated using the algorithm suggested by Weir et al.,[15] (itself an adaptation of that proposed by Weibe et al.[16]) and in accordance with Cochrane recommendations.[17] In summary, we will attempt to apply one of the following methods in the following hierarchical order: (i) use of algebraic recalculation to recover missing data, (ii) contacting of study authors to retrieve missing data, (iii) use of approximate algebraic calculations based on other study-level measures (e.g., range or quartiles), (iv) use of multiple imputation methods, (v) use of non-parametric summaries, (vi) use of single-imputation methods, (vii) summary of non-pooled data alongside meta-analysed results in the systematic review text (Figure 1). As recommended by the Cochrane handbook, (i) the obtention of missing data based on the methods iii-vii will only happen if missing data occurs in a small proportion of studies and (ii) sensitivity analyses will always be performed to assess the impact of dealing with missing data.[17]

We will perform random-effects meta-analyses of mean differences (MD; if scores are measured using the same scale) or of standardised mean differences (SMD; if scores are measured using different scales) in change-from-baseline values (active treatment *versus* placebo). For outcomes calculated based on the same symptoms and giving the same weight to each symptom but with results presented in different scales (e.g., two studies calculating the TNSS based on the same symptoms, but with one presenting the results on a scale of 0-12 and another on a scale of 0-24), scales will be reconverted into a scale of 0-12 for the TNSS and 0-9 for the TOSS. Separate meta-analyses will be performed for patients with seasonal and perennial allergic rhinitis.

The restricted maximum likelihood approach will be used to estimate between-study variance. Heterogeneity will be assessed by estimating the *p*-value of the Q-Cochran test and by the I^2 statistic. Irrespective of the amount of detected heterogeneity, sensitivity analyses will be performed (i) excluding studies with a high risk of bias, (ii) excluding studies in which algebraic calculations needed to be performed to estimate missing data, (iii) based on the follow-up period of the study and (iv) based on the doses of the drugs being assessed. In the presence of substantial heterogeneity, leave-one-out sensitivity analyses will also be performed.

All analyses will be performed using software R, with the use of the metafor and meta packages.

Patient and Public Involvement statement

There will be no Patient or Public Involvement in this study.

Ethics and dissemination

Ethical considerations will not be required. Results will be disseminated in a peer-review journal. Data can be made available by the corresponding author upon reasonable request.

Discussion

This systematic review and meta-analysis will be a first step to assessing the efficacy of specific intranasal antihistamines and corticosteroids in the treatment of allergic rhinitis. While there will be some limitations in terms of generalisability (e.g., as only RCTs with adults and adolescents will be included) or related to the fact that only comparisons against placebo will be considered, these limitations may be overcome by future complementary studies (e.g., a systematic review of RCTs in paediatric patients or a network meta-analysis on intranasal treatments for allergic rhinitis).

Our study will synthesise data from RCTs to determine the impact of intranasal antihistamines and corticosteroids on nasal symptoms, on ocular symptoms and on the quality of life of patients with allergic rhinitis. In addition, it will enable us to assess the methodological quality and certainty in the body of existing evidence, allowing us to make robust conclusions on the efficacy of these treatments. The findings of this systematic review may support recommendations in future guidelines on allergic rhinitis treatment, as well as lay the basis for a future network meta-analysis, taking into account both direct and indirect comparisons between specific drugs.

Authors' contributions: BSP, RJV, JAF and JB participated in the study design and in the drafting of the protocol manuscript. JB, ACF, NLS, RFS, AF, SGM, AB, LK, TZ and HJS participated in the study design and in the critical revision of the manuscript. JB is the guarantor of the review.

Funding statement: The work of this study has been funded within the context of the Allergic Rhinitis and its Impact on Asthma (ARIA) group.

Competing interest statement:

L. Klimek reports grants from Allergopharma, MEDA/Mylan, ALK Abelló, LETI Pharma, Stallergenes, Sanofi, ASIT biotech, Lofarma Quintiles, AstraZeneca, GSK, and Inmunotk; and personal fees from Allergopharma, MEDA/Mylan, HAL Allergie, LETI Pharma, Sanofi, Allergy Therapeut, and Cassella Med, outside the submitted work.

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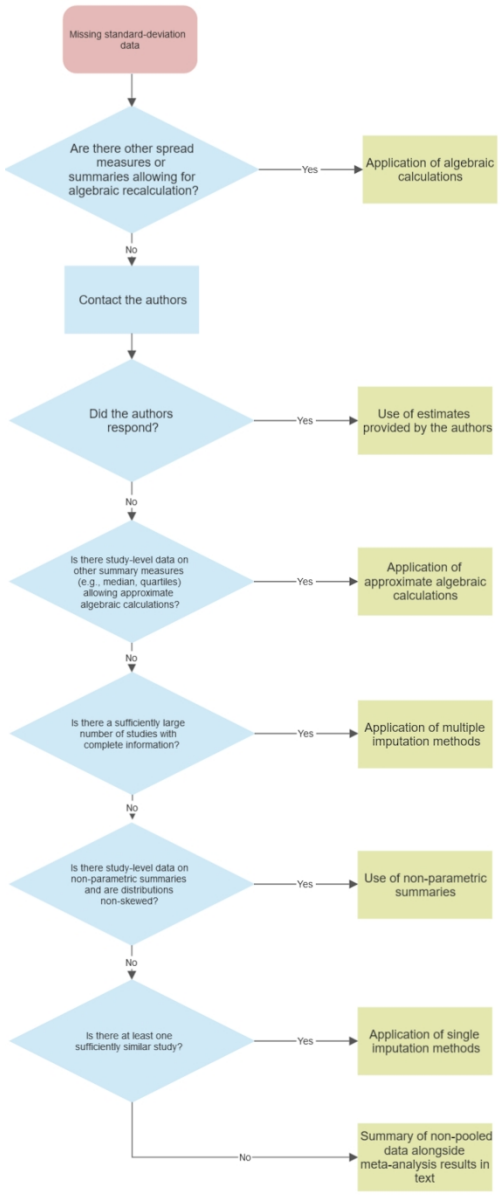

228x543mm (300 x 300 DPI)

Supplementary Table 1. Queries applied in the different bibliographic databases

MEDLINE (Ovid)	
1	azelastin$.mp.
2	azelastine-fluticasone.mp.
3	azeflu.mp.
4	MP-azeflu.mp.
5	(azelastine adj2 fluticasone).mp.
6	dymista.mp.
7	azecort.mp.
8	olopatadin$.mp.
9	olopatadine-mometasone.mp.
10	(olopatadine adj2 mometasone).mp.
11	gsp301.mp.
12	ryaltris.mp.
13	levocabastin$.mp.
14	lexicomp.mp.
15	ciclesonid$.mp.
16	Alvesco.mp.
17	fluticason$.mp.
18	GW685698X.mp.
19	mometason$.mp.
20	beclometason$.mp.
21	budesonid$.mp.
22	triamcinolon$.mp.
23	azelastine.nm.
24	levocabastine.nm.
25	ciclesonide.nm.
26	exp Olopatadine Hydrochloride/
27	exp Fluticasone/
28	exp Mometasone Furoate/
29	exp Beclomethasone/
30	exp Budesonide/
31	exp Triamcinolone/
32	exp Rhinitis/
33	(rhinit$ or rhinoconjunctivit$).mp.
34	exp Allergic Rhinitis/

35	(hayfever or "hay fever" or pollenosis or pollinosis or SAR).mp.
36	(spray or aerosol or powder or inhal$ or solution or turbuhaler or intranasal$ or (intra adj1 nasal) or topical$ or nose or nostril$).mp.
37	exp Administration, Topical/
38	exp Administration, Intranasal/
39	or/1-31
40	or/32-35
41	or/36-38
42	39 and 40 and 41
43	randomized controlled trial.pt.
44	controlled clinical trial.pt.
45	randomized.ab.
46	placebo.ab.
47	clinical trials as topic.sh.
48	randomly.ab.
49	trial.ti.
50	43 or 44 or 45 or 46 or 47 or 48 or 49
51	exp animals/ not humans.sh.
52	50 not 51
53	42 and 52

CENTRAL (CRS Web)

1	(azelastin*):ti,ab,kw OR (azelastine-fluticasone):ti, ab,kw OR (azeflu):ti,ab,kw OR (mp-azeflu):ti, ab,kw OR (azelastine AND fluticasone):ti,ab,kw
2	(dymista):ti,ab,kw OR (azecort):ti, ab,kw OR (olopatadin*):ti,ab, kw OR (olopatadine-mometasone):ti, ab, kw OR ((olopatadine AND mometasone)):ti,ab,kw
3	(gsp301):ti,ab,kw OR (ryaltris):ti,ab,kw OR (levocabastin*):ti,ab,kw OR (lexicomp):ti, ab, kw OR (ciclesonid*):ti,ab,kw
4	(alvesco):ti,ab,kw OR (fluticason*):ti,ab, kw OR (gw685698x):ti, ab, kw OR (mometason*):ti, ab, kw OR (beclometason*):ti,ab,kw
5	(budesonid*):ti,ab,kw OR (triamcinolon*):ti, ab,kw
6	MESH DESCRIPTOR: [Olopatadine Hydrochloride] EXPLODE ALL
7	MESH DESCRIPTOR: [Fluticasone] EXPLODE ALL
8	MESH DESCRIPTOR: [Mometasone Furoate] EXPLODE ALL
9	MESH DESCRIPTOR: [Beclomethasone] EXPLODE ALL
10	MESH DESCRIPTOR: [Budesonide] EXPLODE ALL
11	MESH DESCRIPTOR: [Triamcinolone] EXPLODE ALL

12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	MESH DESCRIPTOR: [Rhinitis] EXPLODE ALL
14	(rhinit*):ti,ab,kw OR (rhinoconjunctivit*):ti, ab,kw
15	MESH DESCRIPTOR: [Rhinitis, Allergic] EXPLODE ALL
16	(hayfever):ti,ab, kw OR ("hay fever"):ti, ab, kw OR (pollenosis):ti,ab,kw OR (pollinosis):ti, ab, kw OR ("SAR"):ti,ab,kw
17	#13 OR #14 OR # 15 OR #16
18	(spray*):ti,ab,kw OR (aerosol):ti, ab, kw OR (powder):ti,ab,kw OR (inhal*):ti,ab, kw OR (solution):ti,ab,kw
19	(turbuhaler):ti, ab,kw OR (intranasal*):ti,ab,kw OR (nasal):ti, ab,kw OR (topical*):ti, ab,kw OR (nose):ti, ab,kw
20	(nostril*):ti,ab,kw
21	MESH DESCRIPTOR: [Administration, Topical] EXPLODE ALL
22	MESH DESCRIPTOR: [Administration, Intranasal] EXPLODE ALL
23	#18 OR #19 OR #20 OR #21 OR #22
24	#12 AND #17 AND #23

Embase

1	(azelastin$ or azelastine-fluticasone or azeflu or MP-azeflu or (azelastine adj2 fluticasone) or dymista or azecort or olopatadin$ or olopatadine-mometasone or (olopatadine adj2 mometasone) or gsp301 orryaltris or levocabastin$ or lexicomp or ciclesonid$ or Alvesco or fluticason$ or GW685698X or mometason$ or beclometason$ or budesonid$ or triamcinolon$).tw.
2	(rhinit$ or rhinoconjunctivit$ or hayfever or "hay fever" or pollenosis or pollinosis).tw.
3	(((spray$ or aerosol or powder or inhal$ or solution or turbuhaler or intranasal$).tw. or intra.mp.) adj1 nasal.tw.) or topical$.tw. or nose.tw. or nostril$.tw. or nasal.tw.
4	1 and 2 and 3
5	randomized controlled trial/
6	controlled clinical study/
7	5 or 6
8	random$.ti,ab.
9	randomization/
10	intermethod comparison/
11	placebo.ti,ab
12	(compare or compared or comparison).ti.
13	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

14 (open adj label).ti,ab.
15 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
16 double blind procedure/
17 parallel group$1.ti,ab.
18 (crossover or cross over).ti, ab.
19 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
20 (assigned or allocated).ti,ab.
21 (controlled adj7 (study or design or trial)).ti,ab.
22 (volunteer or volunteers).ti,ab.
23 human experiment/
24 trial.ti.
25 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 25 not 7
27 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
28 (Systematic review not (trial or study)).ti.
29 (nonrandom$ not random$).ti, ab.
30 "Random field$"ti,ab.
31 (random cluster adj3 sampl$).ti,ab.
32 (review.ab. and review.pt.) not trial.ti.
33 "we searched".ab. and (review.ti. or review.pt.)
34 "update review".ab.
35 (databases adj4 searched).ab.
36 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or
marmoset$1).ti. and animal experiment/
37 37 Animal experiment/not (human experiment/or human/)
38 or/27-37
39 26 not 38
40 4 and 39

Web of Science

1 TS=(azelastin* OR azelastine-fluticasone OR azeflu OR MP-azeflu OR (azelastine NEAR/2 fluticasone) OR dymista OR azecort OR olopatadin* OR olopatadine-mometasone OR (olopatadine NEAR/2 mometasone) OR gsp301 OR ryaltris OR

levocabastin* OR lexicomp OR ciclesonid* OR Alvesco OR fluticason* OR GW685698X OR mometason* OR beclometason* OR budesonid* OR triamcinolon*)

2 TS=(rhinit* or rhinoconjunctivit*) OR TS=(hayfever or "hay fever" or pollenosis or pollinosis or SAR)

3 TS=(spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or (intra NEAR/1 nasal) or topical* or nose or nostril*)

4 TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))

5 TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or

great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or

	ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes)
6	#4 NOT #5
7	#1 AND #2 AND #3 AND #6

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review - Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such - Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author - Pages 1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review - Page 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments - Page 2
Support:		
Sources	5a	Indicate sources of financial or other support for the review - Page 8
Sponsor	5b	Provide name for the review funder and/or sponsor - Page 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol - Page 8
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known - Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) - Page 4
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Supplementary Table 1
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 5

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 5-6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Page 5-6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Pages 4-5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis - Page 6; Page 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised - Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) - Page 6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) - Page 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned - Not applicable. Quantitative synthesis appropriate
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) - Page 6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) - Page 6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.