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

Bernardo Sousa-Pinto,[1,2] Rafael José Vieira,[1,2] Jan Brozek,[3] António Cardoso-Fernandes,[1,2] Nuno Lourenço-Silva,[1,2] Renato Ferreira-da-Silva,[1,2] André Ferreira,[2,4,5] Sara Gil-Mata,[1,2] Anna Bedbrook,[6] Ludger Klimek,[7,8] Joao A Fonseca,[1,2] Torsten Zuberbier,[9,10] Holger J Schünemann ,[3] Jean Bousquet [9,10,11]

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For numbered affiliations see end of article.

Correspondence to
Jean Bousquet;
jean.bousquet@orange.fr

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 (1) assessing patients ≥12 years old with seasonal or perennial allergic rhinitis and (2) 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 Grading of Recommendations Assessment, Development and Evaluation (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 (1) the risk of bias, (2) the follow-up period and (3) the drug dose.

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

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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-based 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 (1) intranasal corticosteroids or fixed combinations of intranasal corticosteroids+antihistamines display higher effectiveness than oral or intranasal antihistamines and (2) 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 (1) focused on a single medication,[6 7] (2) did not specifically provide data for each medication within the same class[8 9] or (3) displayed a different aim (eg, Juel-Berg *et al* sought to compare intranasal corticosteroids vs 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 both the large amount of evidence unpublished in scientific journals and 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 (eg, 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 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 both to acquire pooled meta-analytical estimates on the efficacy of each specific drug, and 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 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 (eg, 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 (1) at least 2 weeks, if assessing patients with seasonal allergic rhinitis or (2) at least 4 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 data set and the AstraZeneca Clinical Trials Website in order to identify potentially unpublished trials. Search queries to be applied are listed in online supplemental 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 purposely-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 (1) the assessed disease (seasonal vs perennial allergic rhinitis), (2) the participants' inclusion and exclusion criteria (as stated in each study description), (3) the data collection period, (4) the places where patients were recruited, (5) the active treatment daily dose, (6) the follow-up period, (7) the number of randomised participants (as well as their age and gender distribution) and (8) 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 postintervention 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 both by reading the study's methods, and 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 (1) the meta-analytical point estimate for each outcome is higher than the minimal important difference, and also (2) if this value is not contained in the respective CI. 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 (1) small and large studies converge on the same effect estimates, (2) there has been an earlier publication of positive results and (3) 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 (± SD) baseline and change-from-baseline value for all outcomes of interest. Any missing information on spread measures (SD, SE 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: (1) use of algebraic recalculation to recover missing data, (2) contacting of study authors to retrieve missing data, (3) use of approximate algebraic calculations based on other study-level measures (eg, range or quartiles), (4) use of multiple imputation methods, (5) use of non-parametric summaries, (6) use of single-imputation methods and (7) summary of non-pooled data alongside meta-analysed results in the systematic review text (figure 1). As recommended by the Cochrane handbook, (1) the obtention of missing data based on the methods (3)–(7) will only happen if missing data occur in a small proportion of studies and (2) 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 vs placebo). For outcomes calculated based on the same symptoms and giving the same weight to each symptom but with results presented in different scales (eg, 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 (1) excluding studies with a high risk of bias, (2) excluding studies in which algebraic calculations needed to be performed to estimate missing data, (3) based on the follow-up period of the study and (4) 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 on 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 (eg, 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 (eg, 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,

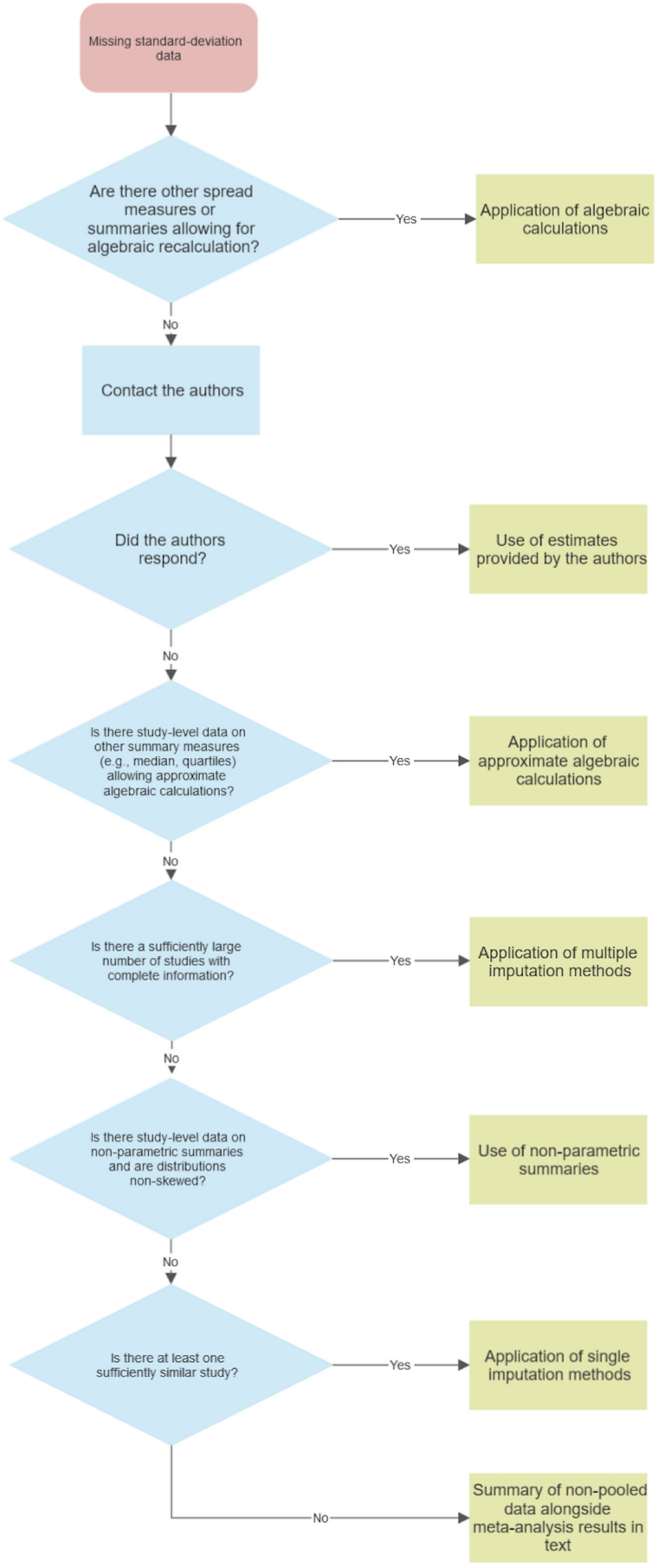

Figure 1 - **Approach that will be followed to estimate missing standard-deviation data from included primary studies**

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.

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.

Author affiliations
[1]MEDCIDS, Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal
[2]CINTESIS@RISE - Health Research Network, MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal
[3]Department of Health Research Methods, Evidence and Impact & Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[4]Unit of Anatomy, Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal
[5]Department of Ophthalmology, Centro Hospitalar Universitário do Porto, Porto, Portugal
[6]MASK-air, Montpellier, France
[7]Department of Otolaryngology, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, Germany
[8]Center for Rhinology and Allergology, Wiesbaden, Germany
[9]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[10]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
[11]ARIA, Montpellier, France

Contributors BS-P, RJV, JAF and JB participated in the study design and in the drafting of the protocol manuscript. JB, AC-F, NL-S, RF-S, AF, SG-M, AB, LK, TZ and HS participated in the study design and in the critical revision of the manuscript. JB is the guarantor of the review.

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ORCID iDs
Holger J Schünemann http://orcid.org/0000-0003-3211-8479
Jean Bousquet http://orcid.org/0000-0002-4061-4766

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