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Review

Efficacy and safety of rupatadine for allergic rhino-conjunctivitis: a systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis

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Abstract

Background:

Allergic rhinitis is a complex inflammatory disease whose pathophysiology involves local and systemic mechanisms. Rupatadine, a molecule with intense antihistaminic activity and with antagonist PAF effects through its interaction with specific receptors, is indicated for the treatment of intermittent or persistent allergic rhinitis and urticaria.

Scope:

This systematic review was aimed at identifying in the most important databases, up to January 2013, the double-blind placebo-controlled randomized trials administering rupatadine in allergic rhinitis. No restriction was introduced for treatment duration and dose, study design, population age, allergen exposition and disease classification. The methodological quality of included studies and risk of bias were systematically assessed. Meta-analysis was performed when possible to summarize information.

Findings:

Seventeen of 413 initially identified records were fully assessed for eligibility. Ten trials involving 2573 patients overall met the inclusion criteria and entered the analysis. Their internal validity was satisfactory. Data synthesis showed that rupatadine is superior to placebo in relieving the overall allergy symptoms on reflective (SMD: -0.37 , 95% CI -0.46 to -0.27 ; $p < 0.00001$) and instantaneous (SMD: -0.41 , 95% CI -0.71 to -0.11 ; $p = 0.007$) assessment, the nasal symptoms considered together (reflective SMD: -0.36 , 95% CI -0.48 to -0.25 ; $p < 0.00001$; instantaneous SMD: -0.39 , 95% CI -0.61 to -0.17 ; $p = 0.0004$) or individually and ocular symptoms. Inter-study heterogeneity was low for the main outcomes and the risk of publication bias was judged as unlikely. A number of secondary endpoints were favorably affected by rupatadine. No difference was observed in the incidence of total adverse reactions between rupatadine and placebo (OR 1.23, 95% CI 0.95 to 1.59; $p = 0.12$).

Conclusion:

Randomized double-blind controlled trials show a favorable risk–benefit ratio in rupatadine for the treatment of allergic rhino-conjunctivitis. This evidence is strengthened when data are pooled in the form of meta-analysis, where accurate and robust effect estimations are derived from a large population.

Introduction

In the last few decades a progressive increase in the incidence of allergic diseases has been observed with regard to different factors including the rise of allergenic substances, the frequency of exposition, and the existence of concurring factors

to the onset of the allergic symptoms¹. The highest prevalence of allergic diseases has been reported in industrialized countries with high standards of living^{2,3}.

The allergic response is currently considered a complex inflammatory reaction involving local and systemic protagonists, like inflammatory mediators, cytokines, chemokines, neuromediators, adhesion molecules and effector cells⁴. Antihistamines play an important role in the treatment of allergic rhino-conjunctivitis (AR) because this disease represents a local inflammatory expression of a systemic disease^{5,6}. In the light of this reason the use of molecules with an effective antihistaminic activity accompanied by a more complete anti-inflammatory action is desirable in order to face not only the clinical symptomatic manifestations but also the inflammatory substrate that sustains disease persistence and progression⁷.

Rupatadine is an antiallergic agent developed to combine a strong inhibitory effect on H1 receptor with a specific antagonism toward the receptor of the platelet activating factor (PAF)^{8,9}. Histamine and PAF are, in fact, two important mediators in the allergic cascade with a synergic and cross-enhancing pro-inflammatory activity¹⁰. PAF increases vascular permeability contributing to the onset of rhinorrhea and nasal congestion. In addition, it exerts a considerable chemotactic activity, promoting the late phase reaction of the allergic response and increasing the activity of eosinophils^{11,12}. For these properties rupatadine has been successfully used in the short and long term treatment of respiratory allergy and urticaria^{13,14}. Rupatadine 10 mg tablets were approved in 22 countries from the EU and Russia for the treatment of seasonal and perennial AR and urticaria. Furthermore, rupatadine is also available in Central and South American and some South-Asia countries. In 2012 a new pediatric dosage form in oral solution (1 mg/ml) for AR in children over 6 years old (>25 kg) has been authorized also in Europe.

Numerous studies have documented the clinical efficacy of rupatadine 10 mg in seasonal and perennial AR and its safety profile. Some of these studies were multicenter randomized double-blind placebo-controlled trials (DBPC RCTs). This kind of experimental model is currently considered the best way to explore the efficacy of a medical intervention and is largely adopted in clinical development plans for phase II and phase III studies¹⁵.

Since heterogeneous findings were reported by the above mentioned researches, performed with different study design and sample size, drug dosages, comparative intervention, patients' age, treatment duration and allergen exposition, the purpose of our investigation was to systematically summarize the available information, thus improving the precision of clinical effect estimations and assessing the risk of bias. The specific 'PICOS' question (population–intervention–comparison–outcome–study design) to be addressed is whether rupatadine is superior to

placebo in relieving the allergic symptoms in patients with AR in the context of DBPC RCTs.

Methods

Eligibility criteria and characteristics

We included any published double-blinded, placebo-controlled, randomized clinical trials (DBPC RCT) involving patients with a history of AR with or without allergic asthma and/or conjunctivitis and IgE sensitization, confirmed by skin prick tests and/or specific IgE assays. No restriction was introduced for treatment duration, dose and formulation (tablet or oral solution), parallel or cross-over study design, population age, allergen exposition or disease classification. Comparison between rupatadine and other pharmacological treatments were not considered.

Search strategy, information sources and study selection

Medical literature was screened up to January 2013 with no restriction of date and language (last search 31 January 2013). The process of trial selection, performed by two independent investigators, included a first phase of title and abstract screening followed by a second phase of eligibility evaluation from the full text format¹⁶. The percentage agreement between the investigators for the assessment of inclusion was calculated by using the κ test and disagreements were solved by discussion¹⁷.

We used the following databases: CENTRAL, MEDLINE, OVID/EMBASE, DARE, SCI-Expanded, UK National Research Register, ISI-web, BIOSIS Previews, SCOPUS, NHS EED, Current Controlled Trials. We also used alternative sources such as references of individual articles and reviews, registers of ongoing trials (<http://clinicaltrials.gov/> and <http://www.actr.org.au/>) and abstracts of relevant meetings. Manufacturers were contacted to assess unpublished data on file in order to avoid publication bias.

The literature searching was based on the exploded subject heading and text words rupatadine (Anti-H1-antagonist/antiallergic agent/H1-antagonist/antihistamine tablet/Rupafin/Rinialer/Rupax/Pafinur/Wystamm/Alergoliber/Ralif/Urtimed) combined with exploded subject headings describing allergic disease (rhinitis/allergic rhinitis/perennial rhinitis/seasonal rhinitis/chronic rhinitis/rhino-conjunctivitis/hay fever/allergy) and focused on target population and study design (humans/clinical studies/randomized clinical studies/comparative studies/controlled clinical trials/multicenter trials/meta-analysis/validation studies/clinical trials ph1-2-3-4/prospective studies).

Data collection process

A data extraction template form was specifically created for the data collection. Each form included the following items: year of publication, language, country, funding, study design, ethical approval, methodological features, participants and disease features, type of exposition, duration of treatment and follow-up with time-points, intervention and control groups, drug dosages, additional/concomitant treatments, sample size calculation, management of loss to follow up and continuous and dichotomous outcome data.

The overall allergy symptoms score (sum of sneezing, rhinorrhea, itchy nose/palate, itchy/watery/red eyes, nasal congestion) was considered as primary outcome. Total nasal symptoms, individual nasal and ocular symptoms, patient's satisfaction and frequency of adverse events (AEs) were used as secondary outcomes. Data were summarized as mean difference on a 12 h or 24 h reflective and instantaneous assessment when possible. Information on nasal flow, markers of nasal or ocular inflammation and quality of life were reported when available and included only in case of a sufficiently large patient population. To obtain missing data we planned to directly contact the respective authors by email. Data presented only in graphic form were digitalized, then converted to numbers using the Digitizelt 1.5.7 program (Digitizelt 2003; Bormann, Braunschweig, Germany), and finally compared when possible with the data on file provided by the authors or manufacturer¹⁸. The extraction was carried out in duplicate by two independent reviewers and differences were reconciled by consensus.

Risk of bias in individual studies and evaluation of validity

The Cochrane Collaboration tool included in the software RevMan 5 was used to assess the risk of bias and the methodological quality of retrieved manuscripts¹⁷. The assessment at study level was based on the estimation of the risk of bias, graded as low, high or unclear for the following items: selection bias, performance bias, detection bias, attrition bias and reporting bias. The judgment was based on the evaluation of: (a) random sequence generation, (b) allocation concealment, (c) blinding, (d) incomplete outcome data and (e) selective outcome reporting.

Data synthesis, summary measures, synthesis of results and heterogeneity assessment

The post-treatment mean and standard deviation (SD) values for both rupatadine and placebo groups were analyzed in each article. In case of different scoring systems

used to evaluate symptoms, we planned to adopt the standardized mean differences (SMD) for the summary statistics. Odds ratios were used to summarize dichotomous outcomes. All results are reported with 95% confidence intervals (95% CI) and all *p*-values are two-tailed. Patient who received at least one dose of drug were considered in the intention-to-treat population (ITT) for efficacy and safety¹⁹.

To assess the statistical heterogeneity among studies we used Cochran's *Q* statistic test and the *I*-square test. When non-substantial heterogeneity was found ($I^2 < 50\%$), data were pooled using a fixed-effects model (FEM), assuming that all studies come from a common population; for $I^2 > 50\%$, the random-effects model (REM) was used, trying to interpret the reasons for the relevant heterogeneity^{20,21}. The analysis was performed using RevMan 5 program (The Cochrane Collaboration, Oxford, UK)²².

Additional analyses and risk of bias across studies

A sensitivity and subgroup analysis, using forest plots and inclusion/exclusion of trials, was planned to compare subsets of data regarding different treatment durations, drug dosages, study design, allergen exposition, patients' age and disease characteristics. Forrest plot analysis was planned to graphically estimate the likelihood of publication bias in the meta-analysis. Funnel-plot and statistical tests to calculate or correct for publication bias were contemplated only when more than 10 trials were included.

Results

Study selection

The primary search through databases identified 413 records; after the removal of duplicates and the addition of records from alternative sources, 387 records were screened. Following the exclusion of documents not related to the topic (review, different outcomes, not placebo controlled, open design, not randomized studies, different disease from AR, pharmacokinetics studies), 17 studies were assessed in full text for potential eligibility^{23–39}. Finally 10 DBPC RCTs satisfied the inclusion criteria and entered the qualitative and quantitative analysis^{23–32} (Figure 1). The κ statistic for inter-rater agreement on study eligibility was 0.65. In six trials some data were not fully reported and could not be extracted from the manuscript^{23,27,28,29,30,31}, thus requiring their acquisition from graphs by digitization, otherwise authors or manufacturers were contacted to obtain raw data.

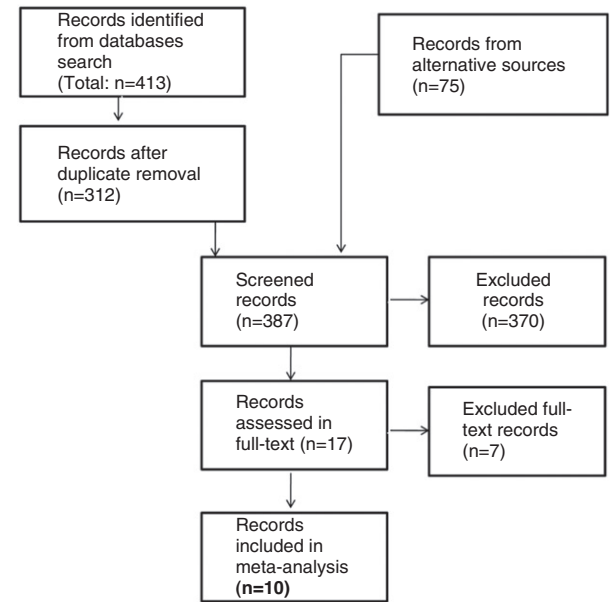


Figure 1. Phases of the systematic search and retrieved articles.

Study characteristics

The characteristics of included trials are reported in detail in Table 1. Ten DBPC RCTs including overall 2573 patients were evaluated for symptom reduction. Four studies investigated the efficacy of rupatadine in seasonal allergic rhinitis (SAR), three in perennial allergic rhinitis (PAR); the remaining three classified the disease according to the ARIA distinction between intermittent and persistent rhinitis (IAR and PER). Median treatment duration was 4 weeks but two trials were under allergen challenge exposition^{24,26}. One study included only children (6–11 years)³¹, five involved patients over 12 years^{23,25,28,32}, and four reported data only from adults^{24,26,27,29}. The age range of participants was 6 to 65 years. Each trial included a median of 266 participants (range: 30 to 543). The reflective assessment (registered every 12 or 24 hours) of overall allergy symptoms was available in eight trials (1650 patients)^{23,25,27–32}; four trials performed an instantaneous assessment (757 patients)^{24–26,32}. Data on individual nasal and ocular symptoms were

Table 1. Characteristics of included trials.

Authors	Design	Disease	Patients entered/ concluded analysis	Age (mean/SD) % males	Comparators	Exposition	Duration
Marmouz <i>et al.</i> ²³	Phase III DBPCR parallel	PAR	282/269 ITT	32 ± 19.93 36%	Rupatadine 10 Rupatadine 20 Cetirizine 10 Placebo	natural	4 weeks
Valero <i>et al.</i> ²⁴	Phase II DBPCR cross-over	PER/IAR	30/30 ITT	28 ± 10 30%	Rupatadine 10 Placebo	challenge	3 + 3 days 14 days wash out
Fantin <i>et al.</i> ²⁵	Phase III DBPCR parallel	PER	543/542 ITT	29 ± 12.89 35%	Rupatadine 10 Cetirizine 10 Placebo	natural	12 weeks
Stuebner <i>et al.</i> ²⁶	Phase II DBPCR cross-over	SAR	45/45 ITT	25 ± 4.8 8.9%	Rupatadine 10 Placebo	6 h challenge Vienna Chamber	8 + 8 days 14 days wash out
Guadaño <i>et al.</i> ²⁷	Phase III DBPCR parallel	SAR	250/243 ITT	33 ± 10.5 41%	Rupatadine 10 Ebastine 10 Placebo	natural	2 weeks
Molina <i>et al.</i> ²⁸	Phase III DBPCR parallel	PAR	223/201 ITT	28 ± 10 47.49%	Rupatadine 10 Ebastine 10 Placebo	natural	4 weeks
Kowalski <i>et al.</i> ²⁹	Phase III DBPCR parallel	PAR	283/283 ITT	30 ± 10.81 47%	Rupatadine 10 Rupatadine 20 Loratadine 10 Placebo	natural	4 weeks
Izquierdo <i>et al.</i> ³⁰	Phase II DBPCR parallel	SAR	178/174 ITT	35 ± 12 68%	Rupatadine 10 Rupatadine 20 Placebo	natural	2 weeks
Potter <i>et al.</i> ³¹	Phase III DBPCR parallel	PER	360/275 ITT	9 ± 1.7 60%	Rupatadine oral solution 2.5–5 mg Placebo	natural	4 weeks
Lukat <i>et al.</i> ³²	Phase III DBPCR parallel	SAR	379/356 ITT	31 ± 12.691 50%	Rupatadine 10 Desloratadine 5 Placebo	natural	4 weeks

DBPCR, double-blind placebo-controlled randomized; PER, persistent allergic rhinitis; PAR, perennial allergic rhinitis; IAR, intermittent allergic rhinitis; SAR, seasonal allergic rhinitis; ITT, intention-to-treat analysis.

available in seven trials^{23,27–32}. Six and five studies reported or permitted calculation of total nasal symptoms score in reflective^{23,27–29,31,32} and instantaneous^{24–26,31,32} acquisition, respectively. Three studies^{23,28,29} reported the outcome Pdmax1 defined as ‘percentage of days during the study for each patient when the score of the daily most severe symptom score was ≤ 1 ’ and six with some kind of patient’s subjective judgment^{23,25,27,30,31,32}. One study reported information on quality of life²⁵ and two on maximum daily total symptoms score^{27,30}. Among studies with challenge test, one reported data on nasal secretion weight after challenge, nasal airflow and visual analogue scale²⁶ and one on nasal volume and nasal nitric oxide²⁴.

Risk of bias within studies

All the included trials were randomized, parallel-group, double-blind, and placebo-controlled. A clear statement about the achievement of patients’ informed consent at enrolment and the respect of ethical requirements was reported in only 8 out of 10 reports^{23–29,32}. All studies based their outcomes assessment on an ITT analysis. Five trials did not provide a study flow diagram to summarize the population’s destiny^{24,26,27,30,31}. The appropriate sample size population was clearly^{23,25–29,32} determined in most trials, although in some of them^{28,29} sample size calculation was calculated based on primary outcomes different from the primary outcome of this systematic review.

The overall assessment for risk of bias, obtained from the individual trial analysis of a) random sequence generation, b) allocation concealment, c) blinding d) incomplete outcome data and e) selective outcome reporting is summarized in Figure 2. Concerning selection bias, the risk is largely unclear because none of the studies provided information on the procedures for allocation concealment and only three^{25,27,29} described how the random sequence was generated. Performance bias was considered at relevant risk in at least four trials^{24,30–32} which did not give detailed information at all on blinding procedures, although this information was guaranteed by the manufacturer (two of the trials were only available in abstract

form). The risk of attrition bias was mainly low, since all trials reported drop-outs and withdrawals and analyzed patients who completed the trial, and the population entered in the ITT analysis was compatible with an appropriate power calculation in all studies except for one²⁴.

Finally, a risk for selective outcome reporting appeared to such extent for what concerns the safety^{23,24,28,32} and the efficacy assessment. In addition, data from some recent studies performed last year were partially available on data on file provided by the manufacturer^{30,31}.

Synthesis of results

Efficacy

Eight trials assessed a daily reflective overall allergy symptoms score^{23,25,27–32}. Out of 1650 analyzed patients for this outcome, 820 received rupatadine 10 mg and showed a significant reduction compared with the 830 patients receiving placebo (SMD: -0.37 , 95% CI -0.46 to -0.27 ; $p < 0.00001$). Among these studies a low heterogeneity was found ($\chi^2 = 8.0$, $p = 0.33$; $I^2 = 12\%$) (Figure 3).

Four trials performed an instantaneous assessment^{24–26,32}. The point estimated for the 375 patients undergoing active treatment was significantly higher compared with the 382 receiving placebo (SMD: -0.41 , 95% CI -0.71 to -0.11 ; $p = 0.007$). Inter-study heterogeneity was significant ($\chi^2 = 10.27$, $p = 0.02$; $I^2 = 71\%$) (Figure 4).

Total nasal symptom reduction was higher in patients receiving rupatadine on the reflective (SMD: -0.36 , 95% CI -0.48 to -0.25 ; $p < 0.00001$) and instantaneous (SMD: -0.39 , 95% CI -0.61 to -0.17 ; $p = 0.0004$) evaluation over 1178 and 1117 subjects, respectively. Heterogeneity was low for the first evaluation and substantial for the second one. Forest plots are reported in Figures 5 and 6.

Pooled data on reflective individual nasal and ocular symptoms were available from seven trials^{23,27–32}. Rupatadine performed better than placebo in reducing rhinorrhea (SMD: -0.30 , 95% CI -0.41 to -0.19 ; $p < 0.00001$), sneezing (SMD: -0.39 , 95% CI -0.52 to -0.26 ; $p < 0.00001$), nasal itching (SMD: -0.21 , 95%

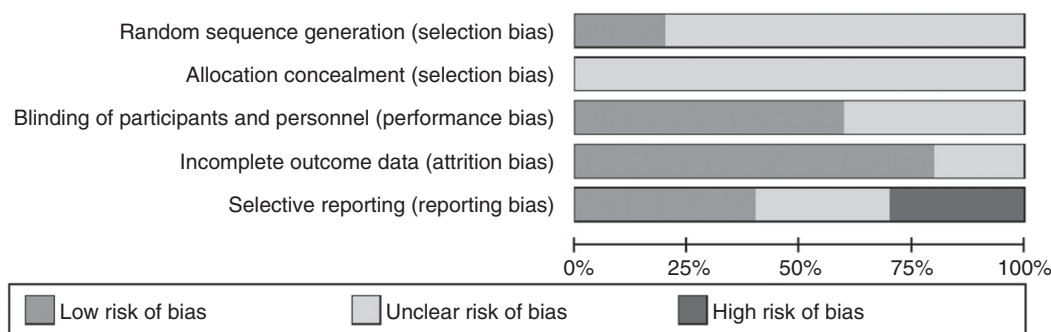


Figure 2. Risk of bias assessment: review authors’ judgments about each risk of bias item presented as percentages across all included studies.

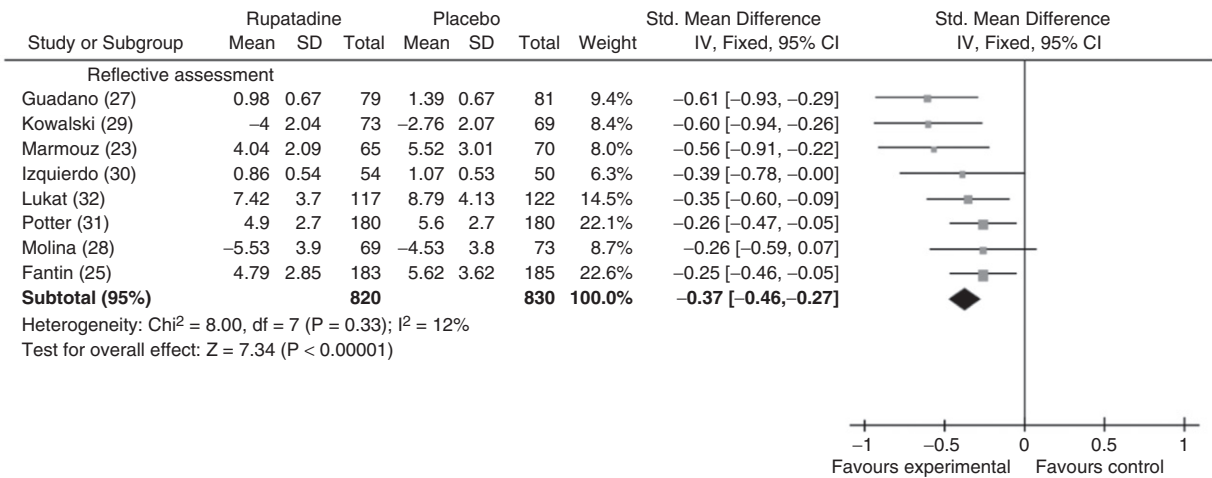


Figure 3. Overall allergy symptoms score: forest plot for reflective assessment.

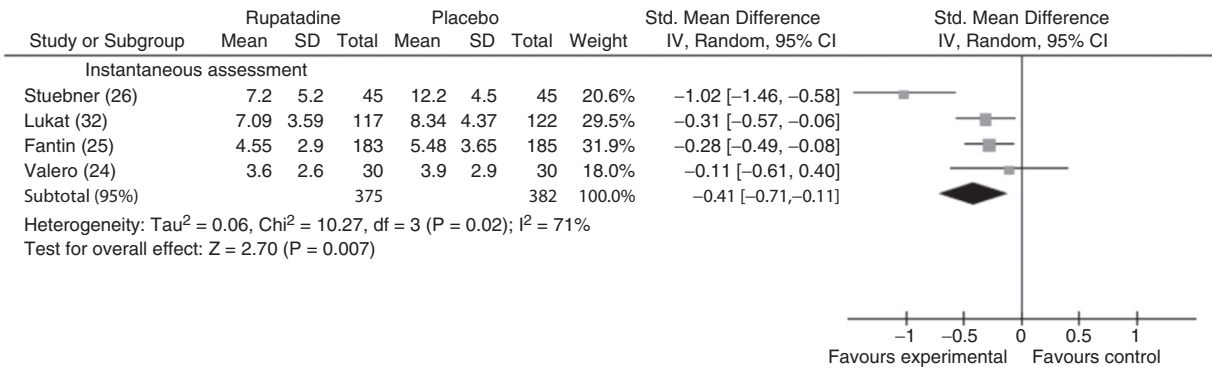


Figure 4. Overall allergy symptoms score: forest plot for instantaneous assessment.

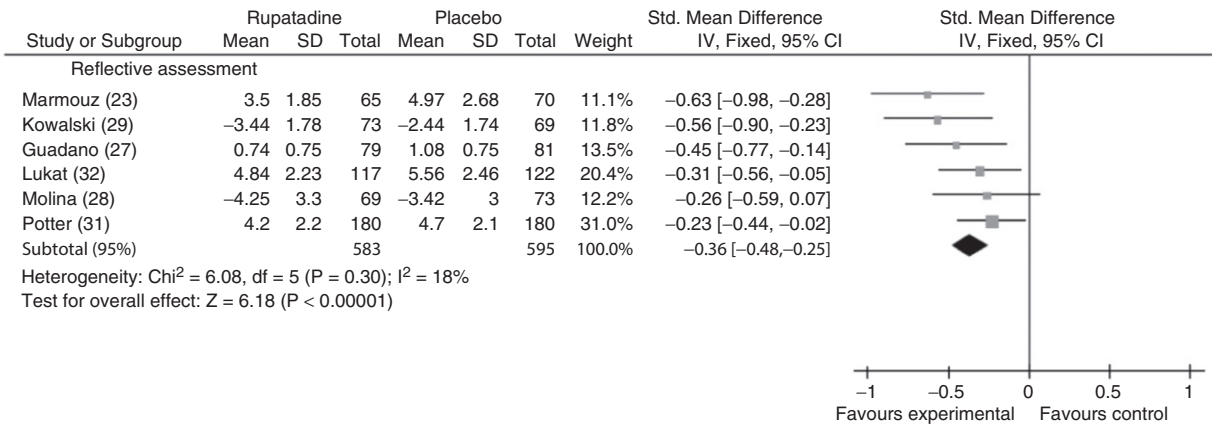


Figure 5. Nasal symptoms score: forest plot for reflective assessment.

CI -0.33 to -0.10; $p = 0.0003$) and nasal obstruction (SMD: -0.25, 95% CI -0.37 to -0.13; $p < 0.0001$). Also, a certain benefit resulted for itchy (SMD: -0.29, 95% CI -0.45 to -0.14; $p = 0.0001$) and watery eyes (SMD: -0.25, 95% CI -0.45 to -0.06; $p = 0.01$) (Figure 7).

Patient's perception of excellent improvement from four trials^{25,27,30,32} was higher in the experimental treatment (OR 1.91, 95% CI 1.40 to 2.60; $p < 0.0001$), as well as the Pdmax1 (SMD: 10.11, 95% CI 2.91 to 17.32; $p = 0.006$) from the three studies evaluating this outcome^{23,28,29}. Patients' quality of life was largely improved

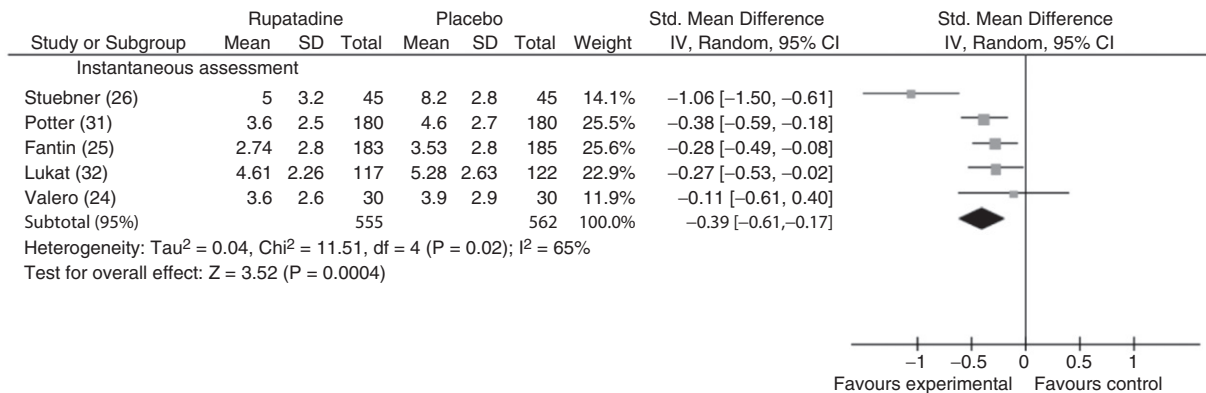


Figure 6. Nasal symptoms score: forest plot for instantaneous assessment.

after 4 (mean difference -8.8% in RQLQ score; $p = 0.016$) and 12 (mean difference -10% in RQLQ score; $p < 0.01$) weeks of treatment compared to placebo²⁵. The maximum value of the total daily symptoms score was lower in patients receiving rupatadine (SMD: -0.26 , 95% CI -0.51 to -0.02 ; $p = 0.21$)^{27,30}. One study²⁶, based on a nasal provocation test in the Vienna chamber, reported no difference ($p = 0.09$) between rupatadine and placebo in the mean nasal airflow reduction after 2 and 6 hours, whereas the mean secretion weights during the 6 hours of exposition and VAS were both consistently lower ($p < 0.001$) when received active treatment. Another challenge study²⁴ documented no difference between rupatadine and placebo in the mean change from baseline of nasal nitric oxide (nNO) and nasal volume during exposition.

Three studies^{23,29,30} included a treatment arm receiving rupatadine 20 mg. In the pooled data, a large benefit to 184 patients was evident for reflective allergy symptoms (SMD: -0.64 , 95% CI -0.85 to -0.43 ; $p < 0.00004$) over placebo (189 patients). Similar findings were found for all four nasal symptoms (SMD: -0.70 , 95% CI -0.94 to -0.45 ; $p < 0.00004$) on the 278 patients compared. The direct comparison between rupatadine 10 mg and rupatadine 20 mg showed no statistically significant advantage of one dose over the other concerning the reflective overall allergy symptoms score (SMD: 0.16 , 95% CI -0.05 to 0.36 ; $p = 0.13$) on 376 patients^{23,29,30} and the total nasal symptoms score (SMD: 0.11 , 95% CI -0.12 to 0.35 ; $p = 0.35$)^{23,29}.

Safety

Information about the occurrence of total AEs during the treatment derives from the observation of six trials^{23,25–28,32} monitoring overall 1136 patients. Taking into account the variance index, no substantial difference in the frequency of total AEs was observed between rupatadine 10 mg (220) and placebo (204) (OR 1.23, 95% CI 0.95 to 1.59; $p = 0.12$) (Figure 8).

A summary statistics risk estimation for all individual AEs was prevented by incomplete reporting in some trials, selectively describing only the most frequent reactions^{23,24,28,32} or those occurring in more than 1–2%, or providing incomplete AEs for patients in any group, or making them available only in abstract form^{30,31}. The most common side effect occurring with antihistamines is sedation. We calculated a number needed to harm (NNH) equal to 13.7 associated with the treatment.

In the study by Marmouz *et al.*²³ the only AE that showed a statistically significant difference compared to placebo was somnolence for both rupatadine 10 mg and 20 mg, but laboratory tests analysis and ECG parameters (QTc interval) did not show any clinical relevant findings between groups. Similar findings were observed by Guadaño *et al.*²⁷. The most frequent AEs reported by Fantin *et al.*²⁵ were headache, somnolence, and rhinopharyngitis with no differences between treatments and placebo. In the study of Molina *et al.*²⁸, headache and somnolence were the most commonly reported AEs in all groups, followed by back pain and fatigue/asthenia, although without statistical significance. No serious events occurred but one patient abandoned the treatment because of localized rash. Kowalsky *et al.*²⁹ found the same but two patients, each receiving rupatadine 10 mg and placebo, showed increases in hepatic enzymes related to the study medication. In addition, in four patients of the study population (one in the placebo group, one in the loratadine group and two in the rupatadine 20 mg group) a QTc prolongation from baseline without clinical relevance was observed in ECG evaluations. Izquierdo *et al.*³⁰ reported no serious AEs and the incidence of somnolence was low in patients receiving active drug (8%) but significantly different between rupatadine 20 mg (14%) and placebo. No trends were noted for blood values and urine analysis. In Potter *et al.*'s pediatric study³¹ AEs were rare in both groups and only headache was reported with higher incidence in the active group whereas ECGs and lab test did not show any relevant findings. No differences were

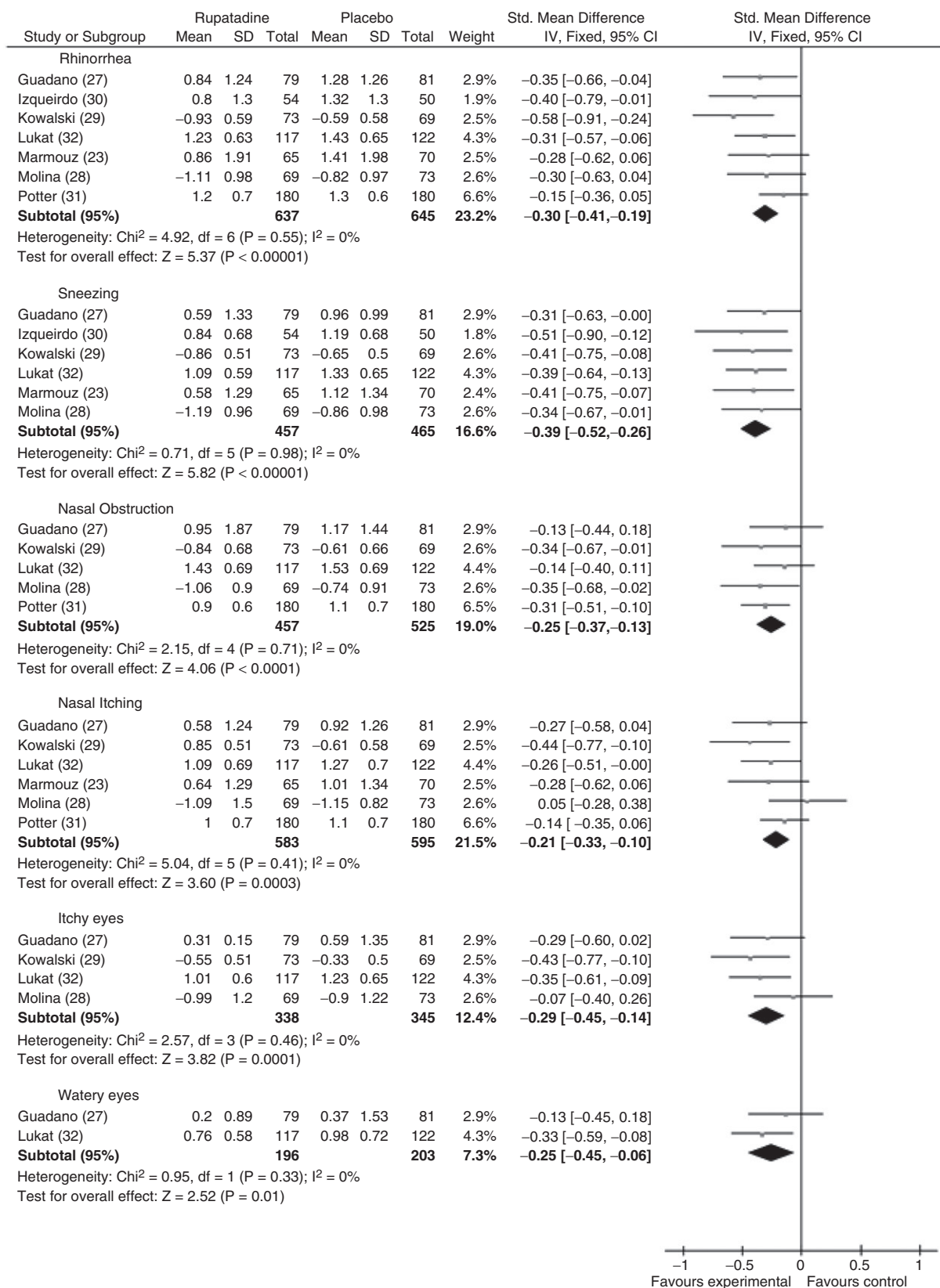


Figure 7. Individual nasal and ocular symptoms score: forest plot for reflective assessment.

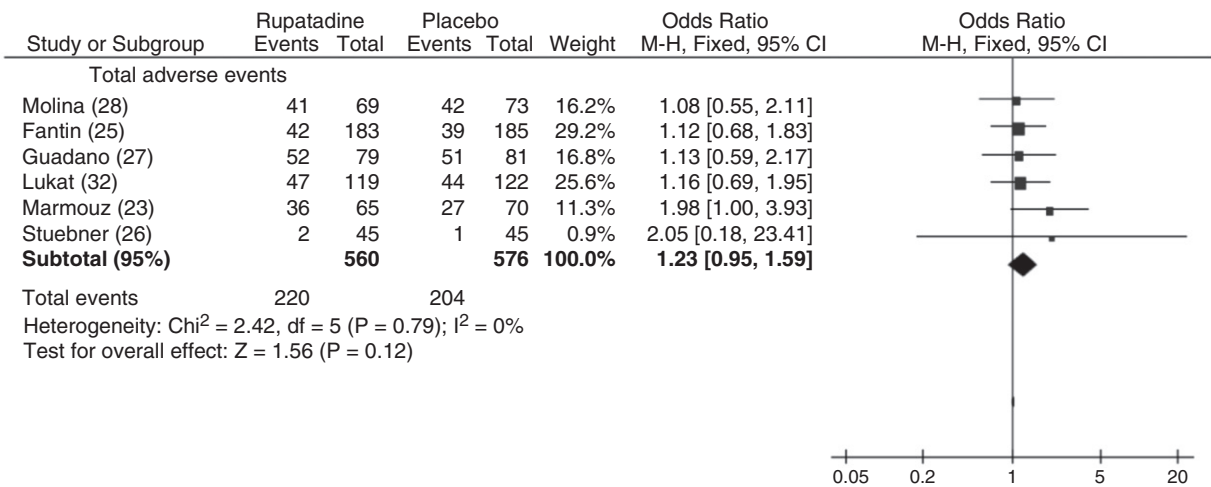


Figure 8. Forest plot for the risk of adverse events.

detected by Lukat *et al.*³² between placebo and rupatadine regarding the percentage of patients who showed an increase of QTc and the incidence of individual diarrhea, headache, somnolence and pharyngo-laryngeal pain. Finally no serious AEs occurred during the challenge studies. Rupatadine was well tolerated, and no severe or unexpected events were reported in the study by Valero *et al.*²⁴. One patient in the active group reported a cough, and one other in the placebo group reported headache and tiredness in Stuebner *et al.*'s study²⁶.

Additional analyses and risk of bias across studies

Subsets of data regarding different subgroups were compared in a post-hoc analysis. Concerning disease characteristics, a significant benefit of rupatadine on reflective overall allergy symptoms score was appreciable for SAR (SMD: -0.40, 95% CI -0.55 to -0.24), PAR (SMD: -0.47, 95% CI -0.66 to -0.28), and PER (-0.26, 95% CI -0.40 to -0.11). For treatment duration, 2 week and 4 week courses were both superior to placebo (SMD: -0.52 and -0.37, respectively). Regarding allergen exposition, study design and patients' age, sub-analyses appeared meaningless since the studies under challenge conditions only assessed symptoms instantaneously and patients' mean age was in the same range in all but one pediatric study. These rather homogeneous results of subset analyses reflect the very low inter-study statistical heterogeneity, apparent for most of the outcomes explored throughout the interpretation of forest plots and the I² statistics. Significant heterogeneity was observed for only the instantaneous assessment of overall and nasal symptoms and can be explained by the clinical heterogeneity of the two challenge studies in delivering treatment with a short

course in cross-over design and with single outcome assessment a few minutes or hours after the forced allergen exposition.

The observation of aligned effect sizes in the forest plots for reflective overall allergy and total nasal symptoms (Figures 3–5) with no substantial variation from one study to the next and no outliers suggests low risk of publication bias. Concerning the funnel plot analysis (Figure 9), the very low number of trials included in this systematic review makes the typical symmetrical distribution rather unlikely. We cannot rule out the possibility that a number of small studies, with effects lower than the average calculated by us, have been neglected by our search or have not been published. Nevertheless, in our opinion, the effects of the largest studies (at the top of the plot) being lower than the average effect, the average estimation itself is unlikely to be driven by the relatively few small studies with larger effect. In addition, concerning the concept of fragility of results related to the impact on statistical significance following small shifts in the number of events, the absence of trials with outlying results suggests a certain robustness of our summary estimations. Since the tests to detect and correct publication bias have a limited value on the small number of studies included, this kind of analysis was avoided⁴⁰. However, when we adjusted with Duval and Tweedie's trim-and-fill method, the aggregated effect size for the primary outcome did not change substantially (SMD: -0.29, 95% CI -0.37 to -0.20; *p* < 0.00001)⁴¹.

Discussion

Systematic reviews are promoted as providing a more robust appraisal of the evidence than traditional narrative

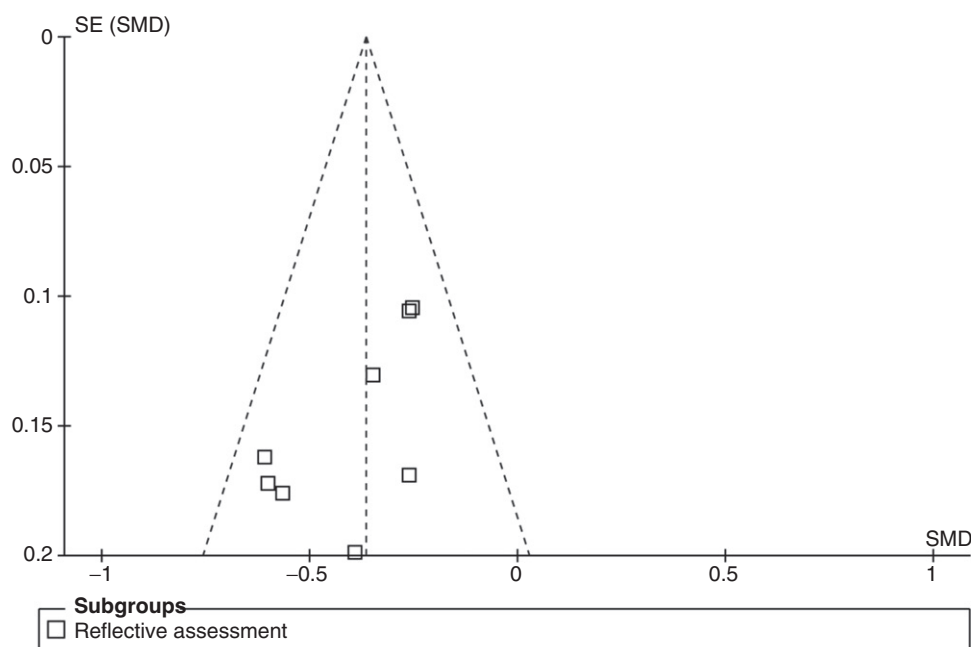


Figure 9. Funnel plot for risk of publication bias assessment for the reflective overall allergy symptoms score.

reviews for their attention given to objectivity, transparency and reproducibility of findings⁴². Our systematic search, conducted following the PRISMA statements checklist⁴³, pointed out that a lot of studies investigated the efficacy of rupatadine in controlling the clinical manifestations of AR but DBPC RCTs represent the best way to explore its efficacy in experimental conditions⁴⁴. Following an extended literature systematic search, we identified ten DBPC RCTs evaluating the effects of rupatadine through several endpoints. A significant benefit was confirmed by the synthesis of the results of individual studies pooled in meta-analysis. Rupatadine 10 mg was superior to placebo in reducing both overall allergy symptoms and total nasal symptoms, assessed reflectively or instantaneously, as well as symptoms considered individually (rhinorrhea, congestion, itching and sneezing). Nasal stuffiness, a bothersome and refractory symptom, was relieved in over 500 patients receiving the active drug. The action of rupatadine on allergic inflammation and activity on nasal PAF receptors was previously demonstrated as particularly pronounced⁴⁵. This clinical evidence shows the potent antiallergic and anti-inflammatory properties that distinguish rupatadine from other antihistamines, which have been documented in *in-vitro* and *in-vivo* studies⁸.

A favorable impact was also observed on ocular symptoms (itchy and watering eyes). The benefit observed in the reflective and instantaneous evaluations suggests the rapid onset of action and its long lasting effect with a once-daily dosing. Finally, one large study confirmed that

rupatadine 1 mg/ml oral solution was also effective in the reduction of nasal and no nasal symptoms in children aged 6–11 years with PAR³¹.

We could not identify a substantial difference when the treatment was delivered to patients with SAR, PAR or PER. Rupatadine 20 mg did not appear significantly more effective than rupatadine 10 mg, but a trend was evident in favor of the higher dosage. This analysis, nevertheless, was based on a population of less than 200 patients per group, likely underpowered to appreciate the difference between two active treatments, in which the lower dose was also high performing. On the other hand, since rupatadine is also indicated for the treatment of urticaria, the possibility of modulating dosages within a safe range represents an added value. In fact, our analysis of the reported total AEs events revealed a comparable incidence between rupatadine 10 mg, rupatadine 20 mg and placebo. The most commonly reported AE in all three options was somnolence, as commonly observed in trials with antihistamines. We notably estimated that about fourteen patients needed to be treated with rupatadine 10 mg in order to observe one case of sedation, confirming the good tolerability of this second generation antihistamine. The NNH is an important measure in evidence-based medicine and helps physicians to decide whether it is prudent to proceed with a particular treatment which may expose the patient to harm while providing therapeutic benefits. In addition, recently, a single dose of rupatadine at four times the recommended dose appeared to be well tolerated retracting a dose–response relationship⁴⁶. No

serious adverse events deserving particular attention were found in our review. No statistically significant changes in electrocardiographic parameters or laboratory values related to any dose of rupatadine were observed. In conclusion, rupatadine 10 mg and 20 mg tablets appear to be safe treatment options, although RCTs do not represent the optimal design to assess drug tolerability, which requires long term evaluation on large populations in the context of post-marketing surveillance studies.

The pooled analysis for the different endpoints, exploring a large population, permitted a more precise detection of the effect size on improvement compared to individual studies. In accordance with the Cohen's scale⁴⁷, a moderate effect could be observed for the overall allergy symptom reduction and the total nasal symptom reduction. The narrow confidence interval and the low inter-study heterogeneity for these outcomes suggest the robustness of these estimations. Inter-study heterogeneity was relevant only for instantaneous assessments owing to the challenge exposition of two trials clearly performed in atypical clinical setting compared to the others. The studies included in our review were likely conducted following an appropriate methodology; however, our risk of bias assessment identified some shortcomings in trial reporting, mainly concerning the procedures for allocation concealment, random sequence generation and blinding strategies. According to the CONSORT statement, details on these aspects are desirable, but in the majority of published trials they are poorly described, mainly for editorial policies^{48,49}. On the other hand, we obtained this information from the authors' and manufacturers' data on file and study protocols. In addition, in some studies selective outcome reporting was apparent for the efficacy and safety endpoints, thus partially downgrading the quality of the evidence, but our overall judgment is inclined to consider their internal validity adequate.

The methodological quality of the evidence captures that degree of confidence in the estimations. There are a number of factors that may influence the strength of a recommendation, such as study design, consistency of results, directness of evidence, and likelihood of bias⁵⁰. In our review, no substantial limitations in study design and execution were found in trials available in full text. However, we could appraise two studies only in abstract form and consulting the data on file from the manufacturer. The summary estimations of effects were consistent for direction and extent along all the endpoints explored. The precision and robustness of our pooled estimations based on a noteworthy sample size and a relatively narrow variability further reinforce our overall positive judgments on the quality of evidence.

Concerning the risk of publication bias, although we did not introduce date or language restrictions, we cannot rule out the possibility that relevant studies have been neglected, thus making the small number of included

trials a weak point of our conclusions⁵¹. However, our attempt to identify publication bias suggested that the threat of severe risk is unlikely.

Conclusions

This systematic review points out that an appreciable risk/benefit ratio for rupatadine emerges from the DBPC RCTs available in literature selected without any sort of restriction. The estimations of effect in improving the clinical condition of patients with allergic rhino-conjunctivitis, observed in adults and children with different disease characteristics, appear robust and sustained by a reasonable quality of evidence. These conclusions have been recently confirmed and strengthened by subsequent phase IV clinical trials aimed at monitoring the tolerability, quality of life and real life effectiveness of this antihistamine⁵².

Transparency

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Declaration of financial/other relationships

E.C. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article. G.W.C. is member of the Uriach scientific advisory board.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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