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REVIEW ARTICLE

As-needed versus regular intranasal corticosteroid for allergic rhinitis: A systematic review and meta-analysis

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Abstract

Background: Daily intranasal corticosteroid (INCS) is recommended for treating allergic rhinitis (AR). Nevertheless, patients are generally not adherent and use it on-demand. The data on the efficacy of as-needed INCS was insufficient.

Objective: We conducted a systematic review and meta-analysis to assess the efficacy of as-needed INCS compared with regular use for AR.

Methods: We searched PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) until May 2021. A pairwise meta-analysis used a random-effects model to estimate the pooled standardized mean difference (SMD). The primary outcome was the total nasal symptom score (TNSS) changes from baseline at 4 and 6 weeks. Secondary outcomes were the changes of individual nasal symptom score and quality-of-life (QoL) score.

Results: We identified five eligible RCTs with a total of 436 patients with AR. Only four studies had adequate data for quantitative synthesis. The TNSS changes of as-needed INCS were not significantly different from the regular use at both 4 (SMD 0.23 [95%CI: -0.14 to 0.60], $p = 0.230$) and 6 weeks (SMD 0.21 [95%CI: -0.02 to 0.44], $p = 0.080$). Most of the changes of individual nasal symptom scores and QoL scores were not significantly different between the two regimens. At 50% or more INCS dose of regular use, as-needed and regular INCS provided a similar efficacy. The treatment effect was, however, less sustained with as-needed INCS.

Conclusion: The efficacy of as-needed use of INCS at 50% of corticosteroid exposure was comparable to regular use in improving nasal symptoms and QoL.

Key words: allergic rhinitis, as-needed, efficacy, intranasal corticosteroid, on-demand, regular, self-adjusted

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Abbreviations:

AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BDP	beclomethasone dipropionate
FF	fluticasone furoate
FP	fluticasone propionate
INCS	intranasal corticosteroid
MF	mometasone furoate
PAR	perennial allergic rhinitis
QoL	quality of life
RCQ-36	Rhinoconjunctivitis Quality of Life-36 questionnaire
RCT	randomized controlled trial
RoB	risk of bias
RQLQ	Rhinitis Quality of Life Questionnaire
SAR	seasonal allergic rhinitis
SD	standard deviation
SMD	standardized mean difference
TNSS	total nasal symptom score

Introduction

Intranasal corticosteroid (INCS) is still the mainstay of treatment in patients with moderate-to-severe or persistent allergic rhinitis (AR), and regular use is recommended.[1,2] Nonetheless, real-world evidence shows that the vast majority of AR patients are not adherent to their medication.[3] They usually stop treatment when they feel better and increase their treatment when uncontrolled.[4] Patients sometimes feel relief despite the absence of INCS use due to the fluctuation of the amount of allergen in their environment. A few types of INCS are currently available over the counter in some countries. As a result, more patients have direct access to medication and usually use it on demand. This patient behavior was observed not only in the use of INCS but also in other AR medications.

Two randomized controlled trials (RCTs) have addressed the efficacy of as-needed use of INCS in treating seasonal AR (SAR).[5,6] They found that as-needed fluticasone propionate (FP) was more effective than placebo in improving nasal symptoms. The symptom score changes from baseline in the as-needed FP group from both studies were 1.5 and 2.02, respectively, exceeding the minimal clinically important difference (MCID) of 0.55.[7] As-needed use of INCS is, therefore, a statistically and clinically effective treatment regimen. Although the full treatment effect of INCS takes up to several days to be achieved, FP was analyzed using 22 RCTs, and it was found that the onset could occur as early as 12 hours after administration.[8] The mechanism of as-needed INCS may partially be explained by its effect on preventing the late phase allergic response and subsequent inflammatory cell infiltrates alongside repeated allergen exposures.[9]

There have been a few studies comparing as-needed and regular use of INCS. Integrated with patient behavior, this on-demand treatment strategy reflects real-life usage and is pragmatic to balance adequate symptom control that is satisfactory for the patient versus the long-term side effects and healthcare costs. However, the efficacy of as-needed INCS is not generally well accepted yet.[10] Thus, we performed a systematic review and meta-analysis aimed to assess the clinical efficacy of as-needed INCS compared with its regular use in treating patients with AR.

Methods

Protocol and registration

We performed a systematic review and pairwise meta-analysis of RCTs to compare the clinical efficacy between as-needed and regular use of INCS in treating patients with AR. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[11] We registered the study protocol with PROSPERO (Registration Number CRD42021246525). Due to the nature of the study, it was considered exempt from ethics approval.

Data sources and strategy

We searched electronic medical and scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), to identify relevant literature from their inception dates to May 31, 2021. We used keywords to determine the appropriate controlled vocabulary terms (e.g., MeSH headings). The systematic search strategy for each database and the number of records identified are provided in **Table E1**. Only studies written in English were included. The authors (C.W., M.S.) reviewed the lists of references from previously reported studies, systematic reviews, and/or meta-analyses. Relevant studies identified from these reference lists that were not included in the previously mentioned database searches were also included. Duplicate records were removed using a citation manager and manual review by the authors.

Study selection

Study selection was based on the presence of all of the following criteria:

1) an RCT study design
2) patients with AR of all ages
3) as-needed use of INCS as the primary intervention
4) regular use of INCS as the control intervention

Exclusion criteria were studies published in languages other than English. Trials with mixed populations of AR and non-AR were excluded unless it was possible to retrieve the required data for the outcomes of AR.

Outcome measures

The primary outcome was the clinical efficacy of INCS measured using total nasal symptom score (TNSS), including nasal congestion, nasal itching, sneezing, and rhinorrhea. The secondary outcomes were the improvement of individual nasal symptom score, quality-of-life (QoL) score, nasal peak inspiratory flow, adverse events, and loss to follow-up. We focused on the outcomes that were measured at 4 and 6 weeks after randomization. We calculated the changes in the measured parameters from baseline to be used in the analysis.

Screening

We searched the titles and abstracts of relevant literature from the pre-specified databases up to May 31, 2021. An open-source machine learning called ASReview was used for priority screening.[12] ASReview needs five relevant and five irrelevant inputs to learn and rearrange the records automatically. Studies by Juniper et al. (1990),[13] Juniper et al. (1993),[14] Khan et al. (2010),[15] Wartna et al. (2017),[16] and Thongngarm et al. (2021)[17] were used as relevant inputs. Two investigators (C.W. and T.T.) screened the rearranged records using ASReview. The screening was stopped after investigators had screened approximately 50% of the records.

Data collection and extraction

The following information was independently extracted from each article by two trained investigators (C.W. and T.T.): study authorship, year of publication, study period, country/location including environmental and pollution factors, language, study design, inclusion and exclusion criteria, population type (i.e., children and/or adults), patient demographics, potential effect modifiers (e.g., cumulative dose of as-needed INCS and type of INCS), sample size, primary objective,

and study conclusion. Summary tables of study characteristics were tabulated to be used for the assessment of study eligibility. We contacted the corresponding author of any study with incomplete outcome data via e-mail. If the authors did not provide any response within 2 weeks, we repeated the request. If no response was received after the second attempt, the data were reported as missing or were imputed as appropriate.

For the primary endpoint (i.e., the mean changes in TNSS) and other continuous endpoints, we extracted the exact mean change values and their standard deviations (SD) from each study if they were readily available. If a study did not directly report the mean change and the SD, we extracted the crude score (mean and SD) at baseline and the score at 4 and 6 weeks. According to the Cochrane Handbook for Systematic Reviews of Interventions,[18] we used the extracted figures to calculate the mean change and SD. If the study did not report the score measured at 4 or 6 weeks, the score within plus or minus a one-week interval from these 2 points (e.g., 3rd week or 5th week) was used if available. For studies that reported the trend of TNSS or other continuous scoring using graphs, we extracted the data from the figures using Digitizelt program (http://www.digitizeit.de/). For studies that did not report the SD or any measure of dispersion, the SD was imputed using the SD from the study with the most similar design and population.[19] For studies that only reported the median and interquartile range, we employed the methods proposed by Luo, et al.,[20] and Wan, et al.[21] to estimate the mean and SD of the samples.

Risk-of-bias assessment

Two authors (P.P. and T.T.) independently assessed the risk of bias of each included study. Any discrepancy in the quality assessment was discussed with the third author (M.S.). The methodological quality of each RCT was evaluated using Risk-of-Bias 2 (RoB2) assessment tools by the Cochrane collaboration.[22] The tool assesses domain-specific quality in 5 aspects: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Study quality was rated qualitatively as "low risk of bias", "high risk of bias", or "some concerns".

Statistical analysis

All analyses were performed using Stata 17 (StataCorp, Texas, USA). We used a traditional approach of pairwise meta-analysis for quantitative synthesis. Heterogeneity of the included studies was evaluated using the Cochrane's Q test and the I-squared statistics (I^2). As all included studies were expected to possess clinical and methodological heterogeneity, DerSimonian and Laird random-effects model was used to pool the estimates. Due to variation in the scoring components and the scaling of the TNSS, the individual nasal symptoms score, and the QoL score, we pooled the estimates from all studies as standardized mean difference (SMD). The interpretation of SMD in our study was based on the definition by Cohen.[23] Treatment effects with an SMD of 0.2, 0.5, and 0.8 were considered small, medium, and large effects, respectively. We also examined the temporal changes in the treatment effects using cumulative meta-analysis. A p-value < 0.05 was considered statistically significant.

Sensitivity and subgroup analysis

In the presence of unacceptably high heterogeneity, the sources of heterogeneity were identified and appropriately managed with subgroup analysis and meta-regression. Potential effect modifiers for subgroup analyses were the study location, the quality of study according to RoB2, age group of the patient, type of INCS (i.e., hydrophilic and lipophilic INCS), and cumulative dose of INCS. A leave-one-out sensitivity analysis was performed to examine the robustness of both the primary and the secondary endpoints. However, subgroup analysis and meta-regression were performed only on the primary outcome of interest.

Strength of evidence

We graded the strength of evidence for the synthesized meta-analytic results by considering the RoB of each study, inconsistency of results, indirectness of evidence, imprecision, and reporting bias following the Grading Quality of Evidence and Strength of Recommendations (GRADE).

Results

Search results and characteristics of included studies

A total of 5,079 records were identified from all databases. Of these records, 2,472 were duplicates and were removed. The remaining 2,607 records were imported into ASReview for machine learning-assisted priority screening. Altogether, two authors (C.W. and M.S.) screened a total of 1,557 records (59.7%) of the inputs. Fifteen records were identified as relevant from ASReview and were sought for retrieval. Three records were excluded as one was a registered protocol, and full-text articles were not retrievable for the other two. The remaining 12 studies were assessed for eligibility, and 5 studies with a total of 436 patients with AR were finally included in the analysis for this systematic review. However, only 4 studies with a total of 286 patients with AR had adequate data for quantitative synthesis. The PRISMA 2020 flow diagram is provided in **Figure 1**.

Characteristics of the included studies, including the study site, type of AR, intervention assigned, age, sex, duration of rhinitis, and baseline TNSS are presented in **Table 1**. The male-to-female proportion of all studies was 0.52:0.48. One study was conducted in children. Two studies were published before 2010 and used hydrophilic INCS, whereas three were published after 2010 and used lipophilic INCS. Details on the inclusion criteria, exclusion criteria, number, and reason of withdrawals of each study are shown in **Table E2**. Details on the outcome of interest, point of outcome measurements, definitions of outcomes, and conclusions of the study are shown in **Table E3**. Details on loss to follow-up that occurred by the week-4 or week-6 measurement time point and the reported side effects are shown in **Table E4**. Only Thongngarm, et al. reported the exact value of cumulative INCS dose in each treatment arm, while Juniper, et al. reported the number of daily puffs in each treatment arm. We illustrate the cumulative INCS dose calculation in each treatment arm from the data provided

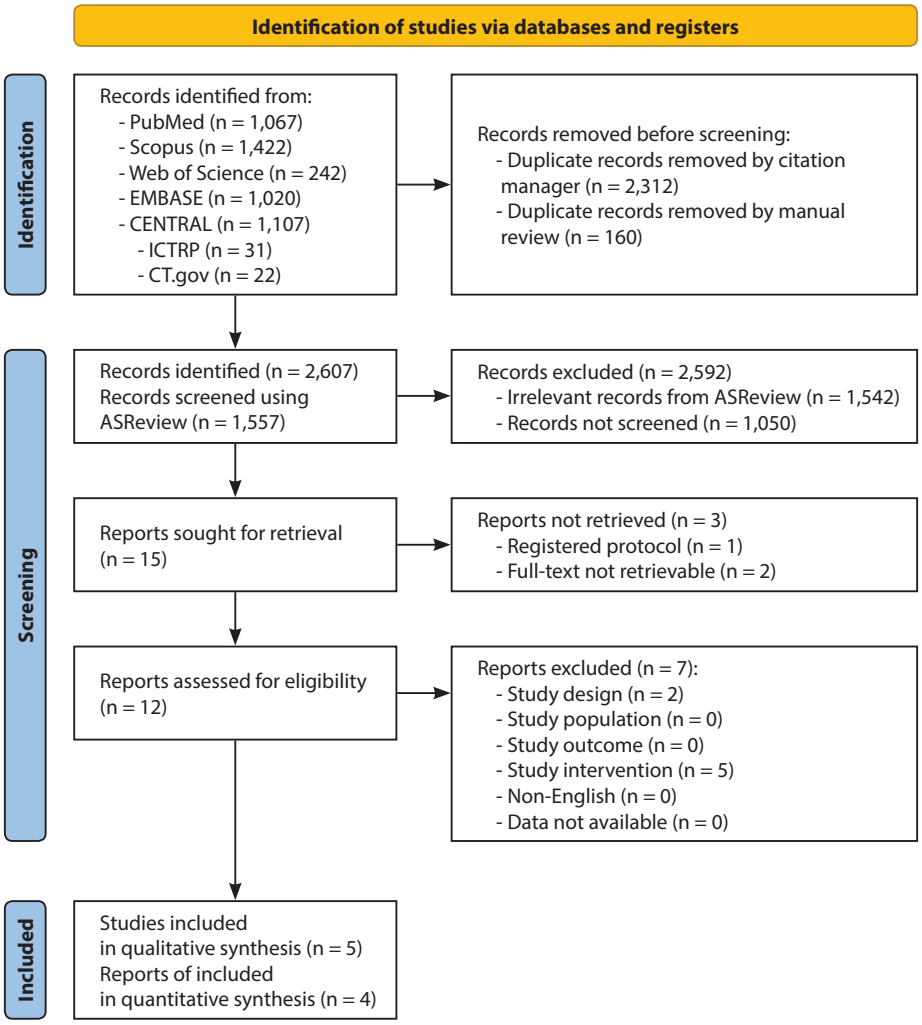

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of included and excluded studies.

Table 1. Characteristics of the included studies.

Studies*	Site of study	Type/duration of RCTs	Type of AR	Study size (n)	Intervention (n)	Age (y)	Female (%)	Duration of rhinitis (y)	Baseline TNSS
Juniper (1990)	Canada	Double blinded/6 wk	SAR	60	As-needed BDP (30)	41.5 ± 13.2¶	45	NR	1.3 (estimated from figure)
					Regular BDP (30)	44.1 ± 12.8¶			
Juniper (1993)	Canada	Open/6 wk	SAR	60	As-needed BDP (30)	16-70¥	37	NR	1.6 (estimated from figure)
					Regular BDP (30)				
Khan (2010)	Saudi Arabia	NR/6 wk	NR	58	As-needed MF (29)	37.3¶	38	2.8¶	6#
					Regular MF (29)	35.7¶		2.9¶	
Wartna (2017)	Netherlands	Single-blinded/12 wk	SAR	150	As-needed FP (52)	11.6¶	48	NR	6.4 ± 2.2¶
					Regular FP (50)				
					As-needed levocetirizine (48)				
Thongngarm (2021)	Thailand	Single-blinded/6 wk	PAR	108	As-needed FF (53)	30 ± 8.4¶	74	15#	8.2 ± 1.6¶
					Regular FF (55)				

Notes: *All studies were performed as single-centered studies; #median; ¶mean or mean ± SD; ¥range; AR, allergic rhinitis; BDP, beclomethasone dipropionate; FF, fluticasone furoate; FP, fluticasone propionate; MF, mometasone furoate; mo, month; n, number; NR, not reported; PAR; perennial allergic rhinitis; SAR; seasonal allergic rhinitis; TNSS, total nasal symptom score; wk, weeks; y, years

in each study and present their ratio to reflect the relative difference in the amount of medication used in **Table E5**.

Risk-of-bias assessment

Based on the Cochrane RoB2, one study was rated with a high risk of bias, while the other four studies were rated as some concerns (**Figure E1**). The study rated as high RoB was due to suspicion of selective reporting of results. The rest of the studies were rated as some concerns of RoB in this domain as no studies had published pre-specified statistical analytic protocol. All studies were rated low RoB for missing data on the endpoints. Only one study was rated as low RoB for the randomization process. The summarized proportions for each domain of the ROB2 are shown in **Figure E2**. Details of the risk-of-bias evaluation of each study are shown in **Table E6**.

Changes in TNSS from baseline

The clinical efficacy of as-needed use of INCS compared to regular use in TNSS changes among the 4 included studies involving 286 patients with AR is illustrated in **Figure 2**. The treatment effect of as-needed use of INCS was not significantly different from regular use in TNSS changes from baseline at both 4 weeks (SMD 0.23 [95%CI: -0.14 to 0.60]; p = 0.230) and 6 weeks (SMD 0.21 [95%CI: -0.02 to 0.44]; p = 0.080). However, the trend of changes in TNSS somewhat favored regular use, especially at 6 weeks after randomization. There was a moderate amount of heterogeneity in pooling the TNSS at 4 weeks. The difference in the treatment effect between as-needed use of INCS and regular use seemed to decrease as more evidence accumulated over time, especially for TNSS changes at 4 weeks (**Figure E3**).

Changes in individual nasal symptom score from baseline

Three studies involving 228 patients with AR were assessed for clinical efficacy of as-needed use of INCS in improving individual nasal symptom score, including nasal congestion, nasal itching, sneezing, and rhinorrhea. For nasal congestion score changes from baseline, the treatment effect of as-needed use of INCS was not significantly different from regular use at 4 weeks (SMD 0.20 [95%CI: -0.06 to 0.47]; p = 0.120). However, the treatment effect at 6 weeks was significantly different in favor of regular INCS (SMD 0.28 [95%CI 0.02, 0.54]; p = 0.040) as shown in **Figure 3**. The pooled results of the remaining aspects are shown in **Figures E4, E5, and E6**. Overall, the treatment effect of as-needed use of INCS was not significantly different from regular use in nasal itching and rhinorrhea scores at both 4 and 6 weeks. The results on the sneezing score were consistent with the findings of the nasal congestion score.

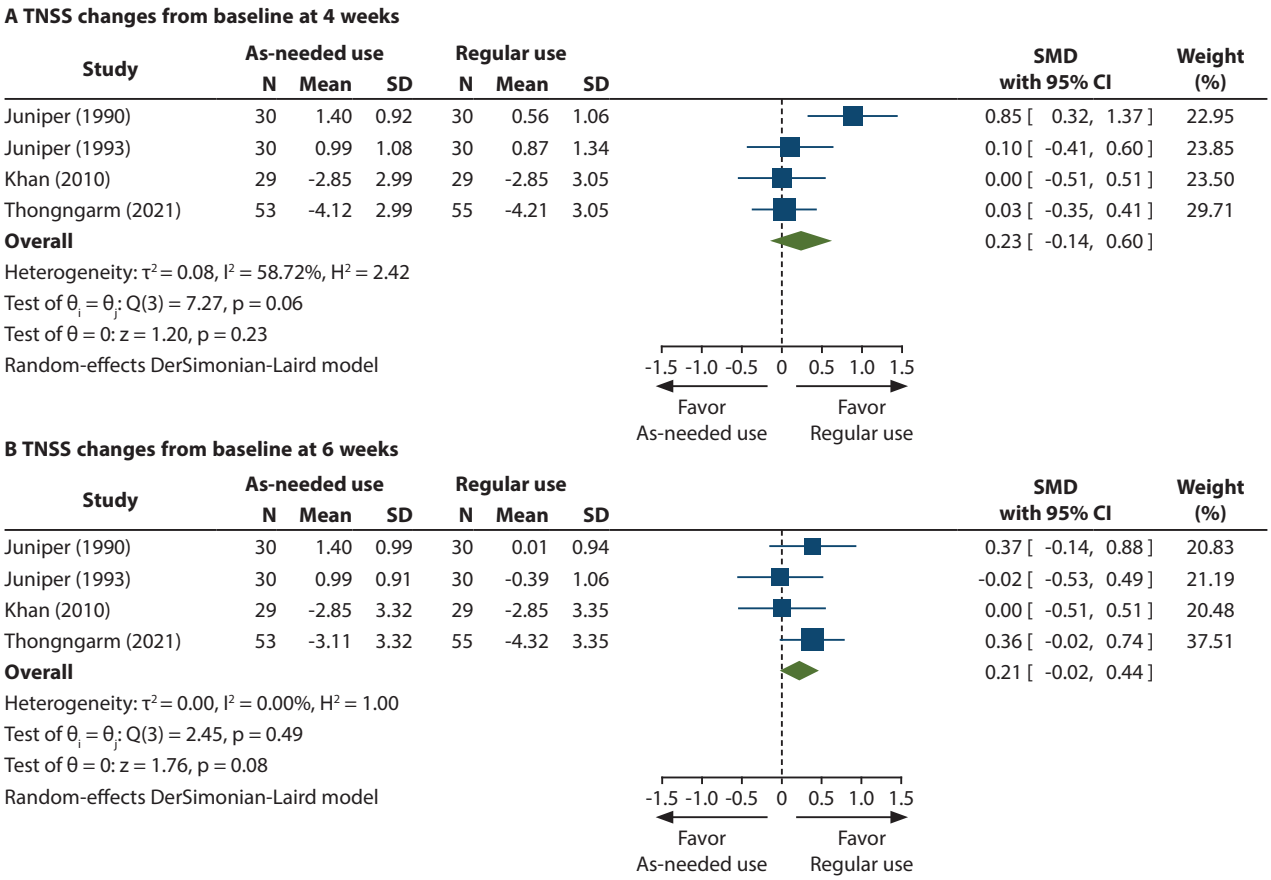

Figure 2. Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, total nasal symptom score changes from baseline at 4 weeks and B, total nasal symptom score changes from baseline at 6 weeks.

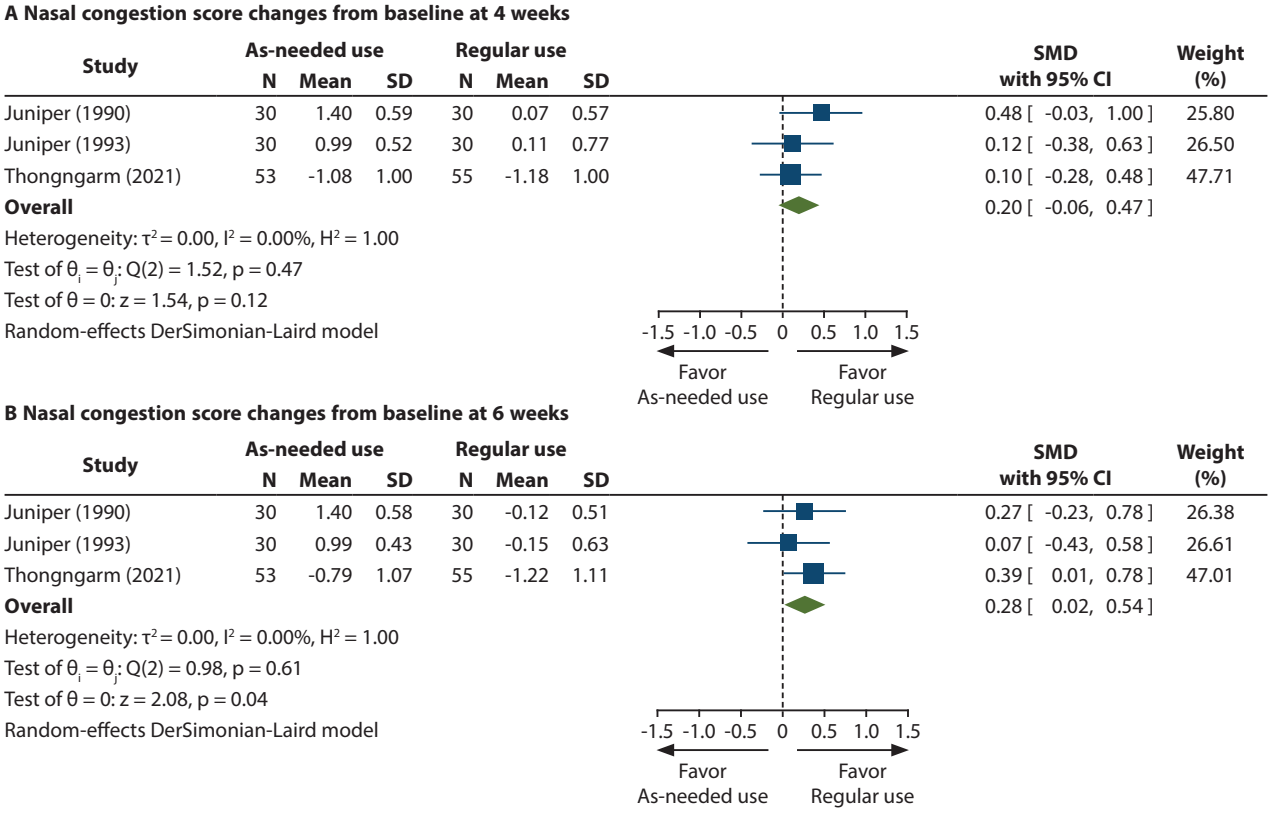

Figure 3. Forest plot showing the pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, nasal congestion score changes from baseline at 4 weeks and B, nasal congestion score changes from baseline at 6 weeks.

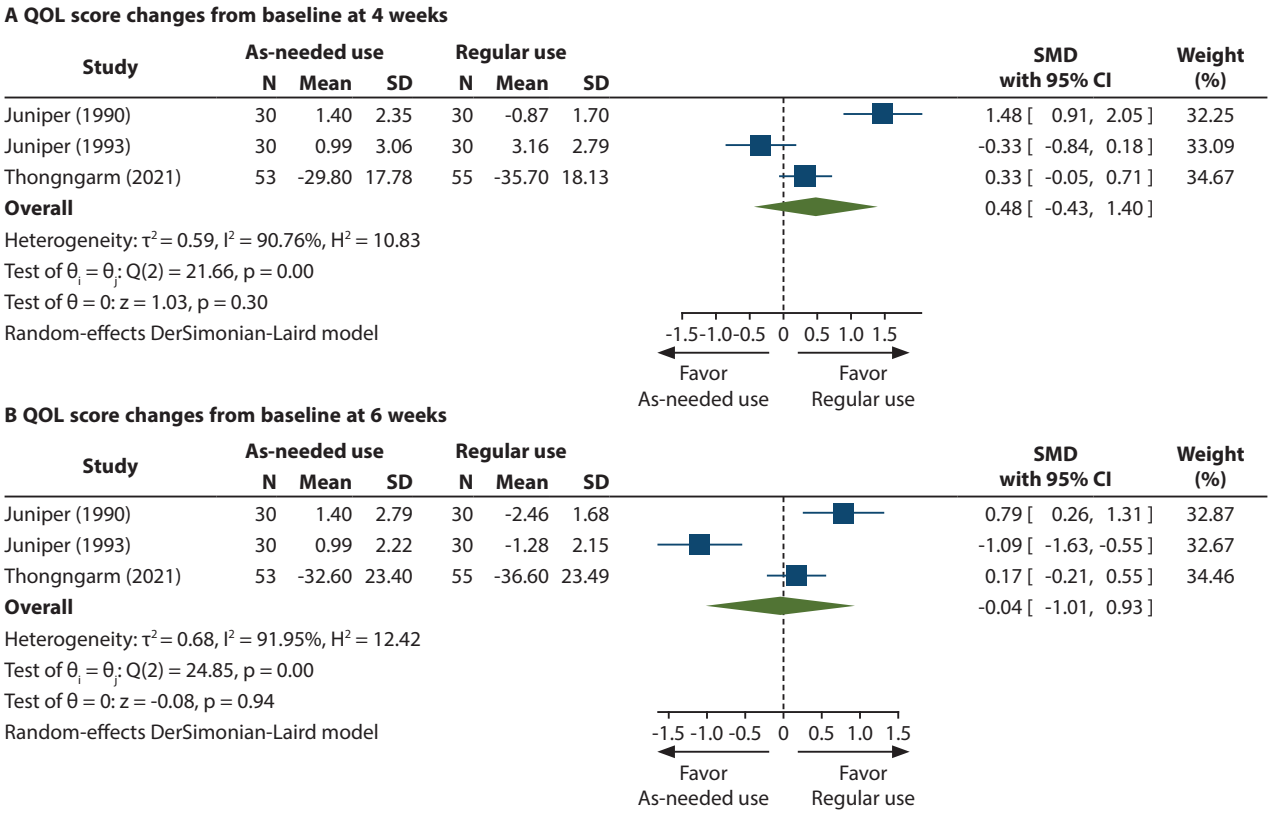

Figure 4. Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, quality-of-life score changes from baseline at 4 weeks and B, quality-of-life score changes from baseline at 6 weeks.

Changes in QoL score from baseline

We used the data from three studies to assess the efficacy of as-needed use of INCS compared to the regular use in improving the overall QoL. The two studies by Juniper, et al. used Rhinitis Quality of Life Questionnaire (RQLQ) as measures for QoL whereas Thongngarm, et al. used Rhinoconjunctivitis Quality of Life-36 questionnaire (RCQ-36). The pooled treatment effect of as-needed use of INCS was not significantly different from the regular use in QoL score changes at both 4 weeks (SMD 0.48 [95%CI: -0.43 to 1.40], p = 0.300) and 6 weeks (SMD - 0.04 [95%CI: -1.01 to 0.47], p = 0.930) as shown in **Figure 4**. However, there was highly significant heterogeneity for both syntheses.

Subgroup and sensitivity analyses

Heterogeneity was observed in the pooling of primary endpoint, and we then performed subgroup analyses to identify the sources of heterogeneity. Based on the available data, we were able to address only three out of six pre-specified effect modifiers, which were studies published before/after 2010, type of INCS, and cumulative dose of INCS. As two studies using hydrophilic INCS were published before 2010, and the other two using lipophilic INCS were published after 2010, only one subgroup analysis was performed. The treatment effect of as-needed use of INCS was not significantly different from the regular use in both subgroups, p = 0.270 and 0.850 at 4 weeks and 6 weeks, respectively (**Figures E7 and E8**). The difference in treatment effect between the two treatment arms at 4 weeks seemed to be minimal when lipophilic INCS was used.

We examined the effect of cumulative INCS dose ratio on the SMD of TNSS changes from baseline at 4 weeks through an exploratory meta-regression. We found a significant association between the cumulative INCS dose ratio and the difference in treatment effect between as-needed use of INCS and regular use (p = 0.015). In other words, the greater the difference in cumulative INCS dose between as-needed use and regular use was, the larger the treatment effect was in favor of regular use. A bubble plot visualizing the trend of association is presented in **Figure 5**.

A leave-one-out sensitivity analysis was performed to examine the robustness of our primary results (**Figure E9**). No study substantially influenced the overall treatment effect for TNSS changes from baseline at 4 and 6 weeks. However, when either the study by Juniper, et al. (1993) or Khan, et al. (2010) was excluded, the conclusion on the difference of treatment effect at 6 weeks changed. **Table E7** presents the leave-one-out sensitivity analysis results for all the secondary endpoints. Most of the sensitivity analysis results were consistent with the overall results except for nasal congestion score and sneezing score changes from baseline at 6 weeks. We did not formally evaluate publication bias as the number of studies included was too few. Evidence summary tables and GRADE evidence profiles are presented in **Table E8**.

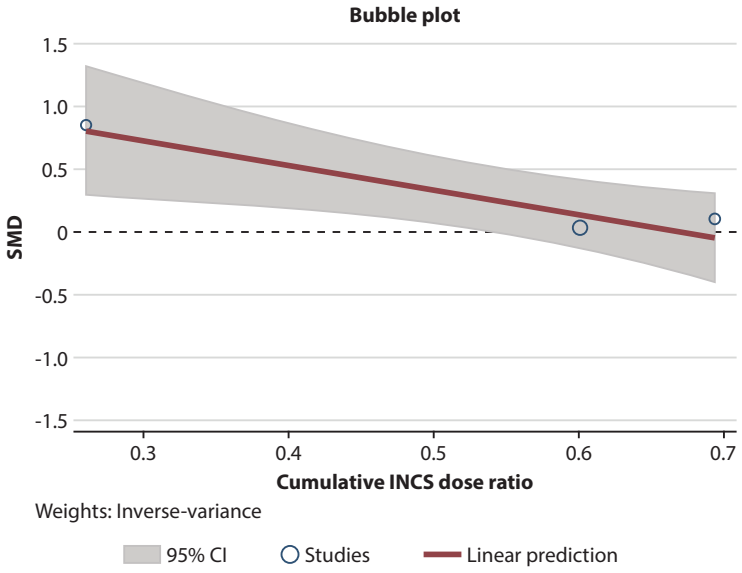

Figure 5. Bubble plot with fitted linear prediction line of the association between the ratio of cumulative intranasal corticosteroid dose and the standardized mean difference of total nasal symptom score changes from baseline at 4 weeks between as-needed intranasal corticosteroid and regular intranasal corticosteroid. Circle markers are sized according to the weights of each study.

Discussion

This systematic review and meta-analysis revealed that as-needed INCS did not result in significantly different treatment outcomes and QoL compared to regular use in patients with AR. Thus, as-needed use has the potential to decrease the cumulative dose of INCS during treatment substantially. However, there was a trend favoring regular use of INCS in improving nasal symptoms at week 6, suggesting a more sustained effect.

Five RCTs addressed the efficacy of as-needed INCS compared with regular use. One study was conducted in children, while the rest were performed in adults. Three studies involved patients with SAR, one involved those with PAR, and one did not report the type of AR. Studies before 2010 yielded high heterogeneity. After that, the others were quite consistent; as a result, the overall heterogeneity did exist. Besides Juniper, et al.'s study in 1990,[13] the rest of recruited studies showed that as-needed INCS is as effective as regular use in improving TNSS.[14-17] The result discrepancy could be explained by a few reasons. First, patients in the as-needed group in Thongngarm, et al.'s and Khan, et al.'s studies were assigned to use regular INCS during the first week, followed by as-needed use for the rest of the study duration. This one-week INCS use was probably crucial to ensure the treatment effect as previous evidence showed that even a 48-hour pretreatment with INCS was able to inhibit allergen-induced nasal hyperreactivity.[9] Nevertheless, in Wartna, et al.'s and Juniper, et al.'s study in 1993, although subjects were initially assigned to use INCS as-needed, their symptom improvement remained comparable to regular use. The results suggest that INCS used as-needed right after symptoms occur had some treatment effect.[9] Second, the types of INCS are different among studies. Beclomethasone dipropionate (BDP) was used in both of Juniper, et al.'s studies, while fluticasone furoate (FF), FP, and mometasone furoate (MF) were used in Thongngarm, et al.'s, Wartna, et al.'s, and Khan, et al.'s studies, respectively. Due to the better pharmacological profiles, the newer lipophilic INCS, including FF, FP, and MF, may be more efficacious than BDP even when used as-needed.[24] This speculative reason needs more studies to compare the efficacy among different INCS when used as-needed since no evidence supports the greater effectiveness of one agent over another.[25] Although most studies yielded comparable efficacy of both INCS-used regimens, there was a trend towards regular use having a more sustained effect.[14,15,17] Of note, improvement in QoL alongside TNSS was not significantly different between the two regimens.[14,17]

Another factor potentially affecting the efficacy of INCS when used as-needed is its cumulative dose. The amount of INCS to represent as-needed use has never been studied except for the cumulative dose of 75% or less as a cut-off established by Dykewicz, et al.[6] The average cumulative dose of as-needed INCS in Thongngarm, et al.'s, Wartna, et al.'s, and Juniper, et al.'s study in 1993 were 51%, 28%, and 39%, respectively, with efficacy comparable in both regimens while Juniper, et al.'s study in 1990 was 13% with results favoring regular use.[13,14,16,17] As expected, the amount of INCS positively correlated with the improvement of TNSS.[26] Based on our exploratory meta-regression, we found that as-needed use at the 50% or more cumulative INCS dose of regular use may result in comparable efficacy to the regular regimen supporting the findings from Thongngarm's study. Of note, the protocols in most of the RCTs for INCS use in the regular group did not allow for lowering of the dose when symptoms were well controlled, so the regular group may have done well with a lower dose while the apparent proportion of INCS use compared to regular use was thus likely overestimated. We suggest that comparing as-needed to regular use may reveal an even lower apparent proportion of INCS use in real-life clinical practice that would reflect that as-needed use is even more practical and effective in the real-life use, in which the patient is allowed to lower their dose.

Given its sustained treatment effect, the regular use of INCS should be encouraged for at least 2-4 weeks[27] until symptoms are well controlled to ensure maximum efficacy and minimize imperceptible residual inflammation,[28] thereby reducing the risk of a flare-up. In patients who are well controlled with regular INCS, the next generation Allergic Rhinitis and its Impact on Asthma (ARIA) guideline recommends step-down treatment to an antihistamine.[1] However, the MASK study[29] demonstrated that the treatment adherence in AR patients was low, so some patients using as-needed antihistamines may experience a symptom flare-up. Interestingly, Kaszuba, et al.[30] reported that as-needed INCS was more effective than as-needed oral antihistamine. Therefore, carefully stepping-down treatment from regular to as-needed INCS could bridge the gap between the INCS and antihistamine treatment steps. Additional advantages of as-needed INCS for AR comprise 1) considerably less corticosteroid exposure that reduces long-term adverse effects[31] and 2) titrating the treatment regimen to the patient's preferred behavior, possibly enhancing their adherence to and acceptability of the treatment. The only concern would be the risk of breakthrough symptoms in some patients. However, choosing an INCS with a relatively rapid onset of action, establishing a written action plan, coaching patients to use INCS right after symptoms occur, and following-up regularly should minimize this drawback. Taking the present study's findings and those of the MASK study[29] together, developing an on-demand treatment concept is a fundamental patient-centered approach to balance acceptable symptom control, long-term side effects, and the cost. This approach is similar to as-needed inhaled budesonide-formoterol in patients with asthma in step 1-2 GINA guidelines.[32] Taking the concept of using as-needed budesonide-formoterol for mild asthma to the ARIA guideline,[1] using as-needed combined INCS/intranasal antihistamine (INAH) in a single bottle for treating allergic rhinitis becomes of interest as its efficacy may be similar to regular INCS. Further studies comparing the efficacy among treatment regimens, including as-needed INCS, as-needed INCS/INAH and regular INCS, to prove our hypothesis are essential. Studies on biomarkers to guide the dose adjustment with the as-needed use of intranasal medication to minimize subtle inflammation are also required.

The strength of this study is in the use of data sources from RCTs specifically designed to answer the research question regarding the comparative efficacy of as-needed and regular use of INCS. This minimized the magnitude of selection bias

and strengthened the internal validity of the pooled estimates. Most of the pooled results were consistent and medically plausible. The likelihood of missing out on eligible studies was low through an extensive searching strategy and priority searching with machine learning. Furthermore, this systematic review and meta-analysis is the first to evaluate the clinical efficacy of as-needed use of INCS compared with regular use in patients with AR to date. However, this study also has several limitations. First, the total number of studies included for evidence synthesis was small. Second, there was substantial clinical and methodological heterogeneity among the five included studies, for instance, the types and severity of AR. The AR severity usually varies considerably among individuals and fluctuates over time, potentially affecting the treatment response. To address this issue, a random-effects model was used for pooling the outcomes. Moreover, pre-specified subgroup analysis and meta-regression were also performed. Third, the meta-regression result reported in this study should be perceived as exploratory as the number of the included studies was less than 10, which was inadequate according to the latest Cochrane Handbook.[18] However, there was still contradicting evidence that a lower number of observations per included covariates might be sufficient.[33] Fourth, most of the data used for quantitative synthesis were not readily available and needed to be extracted from graphs, which might be a threat to the internal validity of the present study. For this reason, we strictly followed the standard guidelines for data extraction and imputation of missing values. Fifth, all continuous outcomes, including TNSS, were pooled as SMD, which might not be simple to interpret.[34] Moreover, the SMD was heavily influenced by the size of the SD of the outcomes in each study. Thus, the pooled SMD could be over- or underestimated easily. However, based on the results of a leave-one-out meta-analysis, our pooled estimates were not substantially influenced by any single study for both the primary and the secondary endpoints at 4 weeks. Finally, all included studies had RoB issues. Most were rated as some concern, and one was rated as high risk. The quality of the pooled evidence can only be as good as the quality of data used for syntheses. Leave-one-out sensitivity analysis by excluding studies with high risk of bias (Juniper, et al., 1993) still showed consistent results for all endpoints at 4 weeks.

In conclusion, as-needed INCS with substantially less corticosteroid exposure was similar to the regular use in improving nasal symptoms and QoL in patients with AR. However, there may be an unpredictable minority who experience breakthrough symptoms due to less sustained treatment effects. Therefore, regular use of INCS should be encouraged until patients are well controlled, and then as-needed INCS could be an alternative step-down option.

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Conflict of interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Ethics approval

Ethics approval was considered exempt due to the nature of systematic review and meta-analysis.

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Supplemental material

Table E1. Searching strategies from (A) PubMed, (B) Cochrane library, (C) EMBASE, (D) Scopus, (E) Web of Science

Database	Step	Search algorithm	Items found
(A) PubMed			
Domain	#1	Rhinitis	46,573
	#2	Allergic rhinitis	32,442
	#3	Hay fever	15,892
	#4	Seasonal allergic rhinitis	14,567
	#5	Perennial allergic rhinitis	8,288
	#6	#1 OR #2 OR #3 OR #4 OR #5	47,676
Intervention	#7	Intranasal administration	20,431
	#8	As-required	6,188
	#9	As-needed	9,104
	#10	On-demand	10,479
	#11	Nasal spray	4,265
	#12	Intranasal spray	2,670
	#13	Intranasal corticosteroids	2,166
	#14	INCS	181
	#15	Beclomethasone	3,957
	#16	Triamcinolone	12,155
	#17	Budesonide	6,588
	#18	Fluticasone	4,792
	#19	Mometasone	1,208
	#20	Ciclesonide	420
	#21	#7 OR #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	73,196
	#22	Nasal symptoms	118,107
	#23	Sneezing	4,349
	#24	Runny nose	6,813
	#25	Stuffy nose	357
	#26	Nasal congestion	3,326
	#27	Rhinorrhea	6,638
	#28	Itchy nose	426
	#29	Nasal itching	1,200
	#30	Nasal symptom score	9,735
	#31	Total nasal symptom score	3,206
	#32	TNSS	307

Table E1. (Continued)

Database	Step	Search algorithm	Items found
(A) PubMed (Continued)			
Outcomes	#33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	124,562
	#34	Randomized controlled trial	705,293
	#35	RCT	26,728
	#36	#34 OR #35	714,378
	#37	#6 AND #21 AND #33 AND #36	1,067
(B) Cochrane library			
Domain	#1	Rhinitis	10,335
	#2	Allergic rhinitis	8,161
	#3	Hay fever	1,480
	#4	Seasonal allergic rhinitis	3,418
	#5	Perennial allergic rhinitis	1,762
	#6	#1 OR #2 OR #3 OR #4 OR #5	11,263
	#7	Intranasal administration	5,284
	#8	As-required	2,642
Intervention	#9	As-needed	4,967
	#10	On-demand	290
	#11	Nasal spray	3,582
	#12	Intranasal spray	1,872
	#13	Intranasal corticosteroids	436
	#14	INCS	75
	#15	Beclomethasone	2,449
	#16	Triamcinolone	3,410
	#17	Budesonide	5,070
	#18	Fluticasone	5,740
	#19	Mometasone	1,381
	#20	Ciclesonide	569
	#21	#7 OR #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	29,432
Outcomes	#22	Nasal symptoms	5,753
	#23	Sneezing	1,746
	#24	Runny nose	544
	#25	Stuffy nose	117
	#26	Nasal congestion	1,588
	#27	Rhinorrhea	1,731
	#28	Itchy nose	238

Database	Step	Search algorithm	Items found
(B) Cochrane library (Continued)			
	#29	Nasal itching	632
	#30	Nasal symptom score	1,807
	#31	Total nasal symptom score	1,283
	#32	TNSS	448
	#33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	7,921
Design	#34	Randomized controlled trial	1,057,980
	#35	RCT	36,122
	#36	#34 OR #35	1,063,137
	#37	#6 AND #21 AND #33 AND #36	1,214
		Trial	1,107
		PubMed	847
		EMBASE	458
		ICTRP	31
		CT.gov	22
(C) EMBASE			
Domain	#1	Rhinitis	110,773
	#2	Allergic rhinitis	46,044
	#3	Hay fever	5,166
	#4	Seasonal allergic rhinitis	5,106
	#5	Perennial allergic rhinitis	4,913
	#6	#1 OR #2 OR #3 OR #4 OR #5	111,646
Intervention	#7	Intranasal administration	46,090
	#8	As-required	8,951
	#9	As-needed	14,687
	#10	On-demand	14,712
	#11	Nasal spray	5,995
	#12	Intranasal spray	4,176
	#13	Intranasal corticosteroids	2,138
	#14	INCS	321
	#15	Beclomethasone	9,743
	#16	Triamcinolone	32,745
	#17	Budesonide	24,211
	#18	Fluticasone	19,310
	#19	Mometasone	5,525
	#20	Ciclesonide	1,723

Table E1. (Continued)

Database	Step	Search algorithm	Items found
(C) EMBASE (Continued)			
	#21	#7 OR #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	157,591
Outcomes	#22	Nasal symptoms	24,644
	#23	Sneezing	9,033
	#24	Runny nose	1,391
	#25	Stuffy nose	348
	#26	Nasal congestion	5,066
	#27	Rhinorrhea	16,373
	#28	Itchy nose	560
	#29	Nasal itching	1,387
	#30	Nasal symptom score	3,134
	#31	Total nasal symptom score	1,778
	#32	TNSS	623
	#33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	45,899
	#34	Randomized controlled trial	935,648
	#35	RCT	47,168
	#36	#34 OR #35	952,622
	#37	#6 AND #21 AND #33 AND #36	1,241
(D) Scopus			
Domain	#1	(allergic AND rhinitis)	94,251
Intervention	#2	(intranasal AND corticosteroids) OR (incs) OR (beclomethasone) OR (triamcinolone) OR (budesonide) OR (fluticasone) OR (mometasone) OR (ciclesonide)	136,381
	#3	(sneezing) OR (runny AND nose) OR (stuffy AND nose) OR (nasal AND congestion) OR (rhinorrhea) OR (itchy AND nose) OR (nasal AND itching) OR (nasal AND symptom AND score) OR (total AND nasal AND symptom AND score) OR (tnss)	42,826
	#4	(randomized AND controlled AND trial) OR (rct)	2,907,497
	#5	#1 AND #2 AND #3 AND #4	2,485
	#6	Only article	1,502
	#7	English article	1,422

Database	Step	Search algorithm	Items found
(E) Web of Science			
Domain	#1	TS = (Rhinitis)	25,914
	#2	TS = (Allergic rhinitis)	20,902
	#3	TS = (Hay fever)	2,575
	#4	TS = (Seasonal allergic rhinitis)	2,873
	#5	TS = (Perennial allergic rhinitis)	1,382
	#6	#1 OR #2 OR #3 OR #4 OR #5	27,601
Intervention	#7	TS = (Intranasal administration)	6,742
	#8	TS = (As-required)	10,272
	#9	TS = (As-needed)	9,719
	#10	TS = (On-demand)	23,096
	#11	TS = (Nasal spray)	4,328
	#12	TS = (Intranasal spray)	1,727
	#13	TS = (Intranasal corticosteroids)	1,281
	#14	TS = (INCS)	200
	#15	TS = (Beclomethasone)	2,314
	#16	TS = (Triamcinolone)	8,196
	#17	TS = (Budesonide)	7,627
	#18	TS = (Fluticasone)	7,495
	#19	TS = (Mometasone)	1,383
	#20	TS = (Ciclesonide)	521
	#21	#7 OR #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	75,806
Outcomes	#22	TS = (Nasal symptoms)	13,221
	#23	TS = (Sneezing)	2,666
	#24	TS = (Runny nose)	582
	#25	TS = (Stuffy nose)	124
	#26	TS = (Nasal congestion)	2,158
	#27	TS = (Rhinorrhea)	2,705
	#28	TS = (Itchy nose)	144
	#29	TS = (Nasal itching)	550
	#30	TS = (Nasal symptom score)	3,807
	#31	TS = (Total nasal symptom score)	1,638
	#32	TS = (TNSS)	323

Table E1. (Continued)

Database	Step	Search algorithm	Items found
(E) Web of Science (Continued)			
	#33	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	18,011
Design	#34	TS = (Randomized controlled trial)	409,318

Database	Step	Search algorithm	Items found
(E) Web of Science (Continued)			
	#35	TS = (RCT)	25,729
	#36	#34 OR #35	416,671
	#37	#6 AND #21 AND #33 AND #36	242

Table E2. Inclusion criteria, exclusion criteria and intervention withdrawal of included studies

Studies	Inclusion criteria	Exclusion criteria	Numbers of withdrawals in each intervention (n) for the whole follow-up period	Reasons for withdrawals (n)
Juniper (1990)	- Subjects with moderate to severe rhinitis during the previous two ragweed-pollen seasons requiring treatment with either INCS, AH or combination. - Subjects had a positive SPT to ragweed extract.	- Subjects had more than a mild sensitivity to fungi - Subjects had perennial rhinitis or polyposis, chronic nasal obstruction or other serious illness. - Subjects had used inhaled or oral corticosteroids or astemizole for at least 1 mo before the study. - Subjects had AIT in the past 12 mo. - Pregnant and nursing women	As-needed BDP (1)	Troublesome symptoms and a dislike of nasal spray (1)
			Regular BDP (0)	
Juniper (1993)	Same as Juniper 1990	Same as Juniper 1990	As-needed BDP (0)	NA
			Regular BDP (0)	
Khan (2010)	Subjects had chronic AR of at least 1 y and had a positive SPT.	- Subjects had paranasal sinus disease, nasal polyps, significantly deviated nasal septum or asthma. - Subjects had taken systemic steroids in the last 30 d. - Subjects had used topical steroids, AH, decongestants or cromolyn in the last 2 wk. - Subjects had received AIT in the last 2 y. - Pregnant and lactating women	As-needed MF (1)	NR
			Regular MF (1)	
Wartna (2017)	- Aged 6-18 y - Sensitization to grass pollen - AR symptom score at least 7/21 in the previous year	- Pregnant or lactating woman - Not being able to speak Dutch sufficiently - Psychosocial problems - Not having internet access for the diary	As-needed FP (6)	- Discontinued medication (2) - Not enough evaluable diary data (4)
			Regular FP (5)	- Discontinued medication (3) - Not enough evaluable diary data (2)
			As-needed levocetirizine (7)	- Discontinued medication (2) - Not enough evaluable diary data (5)
Thongngarm (2021)	- Subjects (age ≥ 18 y) with moderate to severe, persistent PAR - Subjects had positive SPT to indoor allergens (house dust mites, cockroaches, or both). - Mean TNSS ≥ 6 during 7-d before randomization	- Pregnant or lactating woman - Patients with rhinosinusitis, nasal polyps, significant deviated nasal septum, asthma, chronic lung disease, cardiovascular, hepatic, or renal diseases. - Patients taking oral or nasal decongestants within 7 d, INCS within 4 wk, systemic corticosteroid within 8 wk, AH or antileukotriene within 2 wk. - Patients treated with AIT - Patients with URI within 14 d.	As-needed FF (2)	Took prednisolone (1) Misused FF (1)
			Regular FF (3)	Took antihistamine (2) Loss to follow-up (1)

AH, antihistamine; AIT, allergen immunotherapy; AR, allergic rhinitis; BDP, beclomethasone dipropionate; d, day; MF, mometasone furoate; mo, month; FF, fluticasone furoate; NA, not applicable; NR, not reported, PAR, persistent allergic rhinitis; SPT, skin prick test; TNSS, total nasal symptom score; URI, upper respiratory tract infection; wk, week(s); Y, year

Table E3. Outcomes of interest in the included studies and their conclusions

Studies	Interested outcomes	Points of Measurement						Definition of interested outcomes	Findings and conclusions
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6		
Juniper (1990)	Symptom scores	✔	✔	✔	✔	✔	✔	Symptom scores included sneezing, runny nose, stuffy nose, itchy nose, and eye symptom scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.	Regular INCS was more effective than as-needed INCS in improving symptoms and RQLQ. Medication score in the as-needed group was more than the regular group.
	Medication scores	✔	✔	✔	✔	✔	✔	Medication scores included the amount of intervention and rescued medication used in the past 24 hours.	
	RQLQ	✔	✔	✔	✔	✔	✔	RQLQ consisted of 27 items subdivided into 6 domains and measured on a 7-point scale ranging from 0, no trouble at all, to 7, extremely troublesome.	
Juniper (1993)	Same as Juniper 1990	Same as Juniper 1990						Same as Juniper 1990	As-needed INCS was as effective as regular INCS in improving symptoms and RQLQ. Medication score in the as-needed group was similar to the regular group.
Khan (2010)	TNSS	TNSS was compared on each treatment day with the basal score for each intervention.						TNSS was the sum of sneezing, runny nose, stuffy nose, and itchy nose score, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.	As-needed INCS was as effective as regular INCS in improving TNSS and TNCV.
	TNCV	✔	NA	NA	NA	NA	✔	TNCV was measured by acoustic rhinometry.	
Wartna (2017)	- Percentage of symptom-free days - Mean daily total symptom score - Mean eye symptom score - Mean nasal symptom score - Mean total symptom score per symptom (total of 7) - Percentage of symptom-free days for each symptom separately - Proportion of rescue medication-free days and use of rescue medication - Percentage of symptom-low days	Symptom scores measured daily for 12 wk						- Symptom-free days were defined as days with a total symptom score of 0. - A symptom-low day was defined as all the seven symptoms were scored as minor or less, ranging from 1 to 7. - Total symptom score recorded in daily diary assessing four nasal symptoms (sneezing, itchy nose, runny nose, and blockage) and three eye symptoms (tearing eyes, itching eyes, and red eyes), ranging from 0, no symptom to 3, severe.	As-needed INCS, regular INCS, and as-needed OAH are equally effective in the number of symptom-free days.
Thongngarm (2021)	TNSS	✔	✔	✔	✔	✔	✔	TNSS was measured by the sum of 4 individual nasal symptoms.	As-needed INCS was as effective as regular INCS in improving TNSS and RCQ-36 score but nasal congestion score and NPIF are better in the regular group.
	Individual nasal symptom score	✔	NA	NA	✔	NA	✔	Individual nasal symptoms consisted of congestion, rhinorrhea, sneezing, and itching, ranging from 0, no symptom to 3, severe.	
	RCQ-36	✔	✔	✔	✔	✔	✔	RCQ-36 consisted of 36 questions covering 6 dimensions and 2 independent items measured on a 5 point scale (the lower score, the better).	
	NPIF	✔	✔	✔	✔	✔	✔	NPIF was measured in L/min.	

L/min, liters per minute; NA, not applicable; NPIF, nasal peak inspiratory flow; OAH, oral antihistamine; RCQ-36, Rhinoconjunctivitis-specific questionnaire; RQLQ, Rhinoconjunctivitis quality of life questionnaire; TNSS, total nasal symptom score; TNCV, Total nasal cavity volume

Table E4. Loss to follow-up by 4 and 6 weeks of follow-up and the reported side effects of the assigned interventions.

Study (year)	Loss to follow-up at 4 or 6 weeks		Side effects		
	As-needed use	Regular use	As-needed use	Regular use	Overall
Juniper (1990)	0/30	0/30	NR	Occasional bleeding in nasal secretion 1 (3.3%)	Mild and transient
Juniper (1993)	0/30	0/30	NR	NR	NR
Khan (2010)	NR	NR	NR	NR	NR
Wartna (2017)	0/52	0/50	NR	NR	Fluticasone side effect (non-serious) reported by 1 participant as a reason for withdrawal
Thongngarm (2021)	0/53	1/55	Common cold 5 (9.8%) Cough 7 (13.7%) Facial acne 1 (2%) Epistaxis 1 (2%) Headache 1 (2%)	Common cold 8 (15.4%) Cough 6 (11.5%) Facial acne 4 (7.7%) Epistaxis 1 (1.9%) Headache 1 (1.9%)	NR

NR, not reported

Table E5. Cumulative intranasal corticosteroid dose reported in each study.

Study (year)	Cumulative INCS dose (% of total dose)		Cumulative INCS dose ratio (As-needed use/Regular use)
	As-needed INCS	Regular INCS	
Juniper (1990)	105.7 μg/day 105.7/800 in total = 13.21%	405.6 μg/day 405.6/800 in total = 50.7%	13.21/50.7 = 0.26
Juniper (1993)	3.12 puffs/nostril/day 3.12/8 in total = 39%	4.5 puffs/nostril/day (estimated from figure) 4.5/8 in total = 56.25%	39.00/56.25 = 0.69
Khan (2010)	Median 22 puffs (range 16-30)	NR	
Wartna (2017)	102 puffs 102/360 in total = 28.33%	257 puffs 257/360 in total = 71.39%	
Thongngarm (2021)	51%	84.9%	51.00/84.90 = 0.60

INCS, intranasal corticosteroid; NR, not reported

Table E6. Risk of bias assessment by version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) for each included study.

Study 1					
Title	Aqueous beclomethasone dipropionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis (Juniper, 1990)				
Experimental	As-needed use	**Comparator**	Regular use	**Outcome**	TNSS
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	Methods of sequence generation not specified. Methods of randomized concealment not specified.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Well-balanced characteristics between the two groups
	Risk of bias judgment			**Some concerns**	

Table E6. (Continued)

Study 1 (Continued)			
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	One patient in the as-required group might know the assigned intervention.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PY	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	PN	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	modified intention-to-treat (mITT) was used for the analysis
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Only the data from one subject was missing, which was less than 95%.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Same methods of outcome measurements
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Double-blind- Double dummy
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No formal published statistical analytic plan
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	NI	Not enough data to evaluate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Table E6. (Continued)

Study 2					
Title	Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as-needed" use (Juniper, 1993)				
Experimental	As-needed use	**Comparator**	Regular use	**Outcome**	TNSS
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	Methods of randomized were not specified. Methods of concealment were not specified.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Well-balanced characteristics at baseline
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?			Y	Both participants and personnel were aware of the assigned interventions
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			N	No deviations arose
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	All 60 subjects completed the study and were included in the analysis. The authors did not specify the term "intention to treat".
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Data for the outcome were available for all participants randomized
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	The same measurement method and time point were used. There were obvious instructions when symptoms were troublesome.
	4.3 Were outcome assessors aware of the intervention received by study participants?			Y	Participants were not blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			N	Although subjective outcome was used, it is unlikely that the knowledge of the intervention received would influence the assessment of the outcome.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	

Table E6. (Continued)

Study 2 (Continued)			
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No information regarding prespecified analytic plan
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	No information regarding severity and duration of each symptom, which was collected as specified in the methods section
	5.3 ... multiple eligible analyses of the data?	PY	Results of multiple regression analysis were not reported
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Study 3					
Title	Daily versus self-adjusted dosing of topical mometasone furoate nasal spray in patients with allergic rhinitis: randomized, controlled trial (Khan, 2010)				
Experimental	As-needed use	**Comparator**	Regular use	**Outcome**	TNSS
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	Methods of randomization were not specified. Methods of concealment were not specified.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Well balanced characteristics
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?			Y	Unblinded study
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NI	The exclusion of patients was unclear.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	Assuming the authors used modified ITT or ITT in the analysis. However, the exclusion of two patients was questionable (whether pre-randomization or post-randomization).
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	

Table E6. (Continued)

Study 3 (Continued)			
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Almost all data (except for two patients excluded)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Participants were not blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Although subjective outcome was used, it is unlikely that the knowledge of the intervention received would influence the assessment of the outcome.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Prespecified statistical analysis plan not available
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes were reported
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Study 4					
Title	Symptomatic treatment of pollen-related allergic rhinoconjunctivitis in children: randomized controlled trial (Wartna, 2017)				
Experimental	As-needed use	**Comparator**	Regular use	**Outcome**	TNSS
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Detail on allocation concealment was not stated.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	Balanced, a little difference in the proportion of asthma between the 2 groups
	Risk of bias judgement			**Some concerns**	

Table E6. (Continued)

Study 4 (Continued)			
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Patients, their GP, and the research assistants visiting the patient are aware of the patient's medication use; those assessing the outcomes are blinded. However, the focus was on patient-reported outcomes.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PY	Due to unblinded nature of the trial
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Y	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Y	Well balanced, non-differential exclusion
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PN	The authors claim their analysis to be ITT; however, patients who discontinued their medications were also excluded.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN	less than 5% were excluded due to discontinued medication in each arm. balanced exclusion
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Data were available for almost all participants. Missing about 10%
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Outcome assessors were participants who were not blinded to the assigned interventions
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Although subjective outcome was used, it is unlikely that the knowledge of the intervention received would influence the assessment of the outcome.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Prespecified statistical analysis plan not available
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All results were reported
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Table E6. (Continued)

Study 5					
Title	As-Needed Versus Regular Use of Fluticasone Furoate Nasal Spray in Patients with Moderate to Severe, Persistent, Perennial Allergic Rhinitis: A Randomized Controlled Trial (Thongngarm, 2021)				
Experimental	As-needed	**Comparator**	Regular	**Outcome**	TNSS
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	A computer-generated random sequence was used. Concealment with central randomization.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Well-balanced characteristics
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?			Y	Participants were aware of the assigned intervention. Study personnel was blinded to the assigned intervention. Co-medications are not allowed.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PY	Due to unblinded nature of the trial
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			Y	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			PY	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	Both ITT and PP were used in the analysis. The results of both methods were consistent.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Almost all were included. Sensitivity analysis was presented.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	
	4.3 Were outcome assessors aware of the intervention received by study participants?			Y	Outcome assessors were participants who were not blinded to the assigned interventions
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			N	Although subjective outcome was used, it is unlikely that the knowledge of the intervention received would influence the assessment of the outcome.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	

Table E6. (Continued)

Study 5 (Continued)			
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Prespecified statistical analysis plan not available
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All results were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were consistent with prespecified pan
	Risk of bias judgment	**Some concerns**	
Overall bias	**Risk of bias judgment**	**Some concerns**	

Table E7. Leave-one-out sensitivity analysis results for primary and secondary endpoints.

Endpoints	Omitted study	SMD (95%CI)	*P*-value
TNSS changes from baseline at 4 weeks	Overall (not omit)	0.23 (-0.14, 0.60)	0.232
	Juniper (1990)	0.04 (-0.22, 0.30)	0.761
	Juniper (1993)	0.27 (-0.24, 0.79)	0.292
	Khan (2010)	0.30 (-0.19, 0.79)	0.224
	Thongngarm (2021)	0.31 (-0.21, 0.83)	0.238
TNSS changes from baseline at 6 weeks	Overall (not omit)	0.21 (-0.02, 0.44)	0.078
	Juniper (1990)	0.17 (-0.10, 0.43)	0.213
	Juniper (1993)	0.27 (0.01, 0.53)	0.043
	Khan (2010)	0.26 (0.00, 0.52)	0.048
	Thongngarm (2021)	0.12 (-0.18, 0.41)	0.435
Nasal congestion score changes from baseline at 4 weeks	Overall (not omit)	0.20 (-0.06, 0.47)	0.124
	Juniper (1990)	0.11 (-0.19, 0.41)	0.485
	Juniper (1993)	0.25 (-0.12, 0.62)	0.181
	Thongngarm (2021)	0.30 (-0.06, 0.66)	0.103
Nasal congestion score changes from baseline at 6 weeks	Overall (not omit)	0.28 (0.02, 0.54)	0.037
	Juniper (1990)	0.28 (-0.03, 0.58)	0.073
	Juniper (1993)	0.35 (0.05, 0.66)	0.024
	Thongngarm (2021)	0.17 (-0.18, 0.53)	0.342
Nasal itching score changes from baseline at 4 weeks	Overall (not omit)	-0.07 (-0.33, 0.19)	0.595
	Juniper (1990)	-0.09 (-0.40, 0.21)	0.544
	Juniper (1993)	-0.14 (-0.44, 0.17)	0.377
	Thongngarm (2021)	0.06 (-0.30, 0.41)	0.756
Nasal itching score changes from baseline at 6 weeks	Overall (not omit)	-0.04 (-0.30, 0.22)	0.773
	Juniper (1990)	0.00 (-0.30, 0.30)	0.997
	Juniper (1993)	-0.06 (-0.36, 0.24)	0.704
	Thongngarm (2021)	-0.06 (-0.42, 0.29)	0.727
Sneezing score changes from baseline at 4 weeks	Overall (not omit)	0.27 (-0.33, 0.86)	0.383
	Juniper (1990)	-0.00 (-0.34, 0.33)	0.990
	Juniper (1993)	0.50 (-0.27, 1.27)	0.200
	Thongngarm (2021)	0.34 (-0.77, 1.46)	0.545
Sneezing score changes from baseline at 6 weeks	Overall (not omit)	0.39 (0.06, 0.71)	0.019
	Juniper (1990)	0.29 (-0.17, 0.75)	0.217
	Juniper (1993)	0.53 (0.23, 0.84)	0.001
	Thongngarm (2021)	0.31 (-0.25, 0.86)	0.283

Table E7. (Continued)

Endpoints	Omitted study	SMD (95%CI)	*P*-value
Rhinorrhea score changes from baseline at 4 weeks	Overall (not omit)	0.16 (-0.10, 0.42)	0.230
	Juniper (1990)	0.10 (-0.20, 0.41)	0.502
	Juniper (1993)	0.16 (-0.14, 0.47)	0.288
	Thongngarm (2021)	0.23 (-0.13, 0.59)	0.208
Rhinorrhea score changes from baseline at 6 weeks	Overall (not omit)	0.11 (-0.15, 0.37)	0.424
	Juniper (1990)	0.09 (-0.33, 0.50)	0.684
	Juniper (1993)	0.20 (-0.10, 0.51)	0.190
	Thongngarm (2021)	-0.04 (-0.40, 0.32)	0.835

Endpoints	Omitted study	SMD (95%CI)	*P*-value
QOL score changes from baseline at 4 weeks	Overall (not omit)	0.48 (-0.43, 1.40)	0.303
	Juniper (1990)	0.02 (-0.62, 0.66)	0.944
	Juniper (1993)	0.88 (-0.24, 2.01)	0.124
	Thongngarm (2021)	0.57 (-1.20, 2.34)	0.528
QOL score changes from baseline at 6 weeks	Overall (not omit)	-0.04 (-1.01, 0.93)	0.938
	Juniper (1990)	-0.44 (-1.68, 0.79)	0.481
	Juniper (1993)	0.45 (-0.15, 1.05)	0.142
	Thongngarm (2021)	-0.15 (-1.99, 1.69)	0.873

Abbreviations: CI, confidence interval; QOL, quality of life; TNSS, total nasal symptom score; SMD, standardized mean difference.

Table E8. GRADE evidence profile of as-needed intranasal corticosteroid compared with regular intranasal corticosteroid use for allergic rhinitis

Certainty assessment							Summary of findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Regular use INCS	With As-needed use INCS		Risk difference with As-needed use INCS
TNSS changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: TNSS)										
286 (4 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	144	142	-	SMD 0.23 SD higher (0.14 lower to 0.60 higher)
TNSS changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: TNSS)										
286 (4 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	144	142	-	SMD 0.21 SD higher (0.02 lower to 0.44 higher)
Nasal congestion score changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: Nasal congestion score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.2 SD higher (0.06 lower to 0.47 higher)
Nasal congestion score changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: Nasal congestion score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.28 SD higher (0.02 higher to 0.54 higher)

Table E8. (Continued)

Certainty assessment							Summary of findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Regular use INCS	With As-needed use INCS		Risk difference with As-needed use INCS
Nasal itching score changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: Nasal itching score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.07 SD lower (0.33 lower to 0.19 higher)
Nasal itching score changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: Nasal itching score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.04 SD lower (0.3 lower to 0.22 higher)
Sneezing score changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: Sneezing score)										
228 (3 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	VERY LOW	115	113	-	SMD 0.27 SD higher (0.33 lower to 0.86 higher)
Sneezing score changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: Sneezing score)										
228 (3 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	VERY LOW	115	113	-	SMD 0.39 SD higher (0.06 higher to 0.71 higher)
Rhinorrhea score changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: Rhinorrhea score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.16 SD higher (0.1 lower to 0.42 higher)
Rhinorrhea score changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: Rhinorrhea score)										
228 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	LOW	115	113	-	SMD 0.11 SD higher (0.15 lower to 0.37 higher)
Quality of Life score changes from baseline at 4 weeks (follow up: 4 weeks; assessed with: Quality of Life score)										
228 (3 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	VERY LOW	115	113	-	SMD 0.48 SD higher (0.43 lower to 1.4 higher)
Quality of Life score changes from baseline at 6 weeks (follow up: 6 weeks; assessed with: Quality of Life score)										
228 (3 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	VERY LOW	115	113	-	SMD 0.04 SD lower (1.01 lower to 0.93 higher)

CI: Confidence interval; SMD: Standardised mean difference

Explanations

[a] Most studies were at some concerns of risk of bias. One study was rated high risk of bias.

[b] A low number of included studies. Each study had a low number of included patients.

[c] Inconsistency in results among the included studies.

Figure E1. Risk-of-bias assessment of the included studies

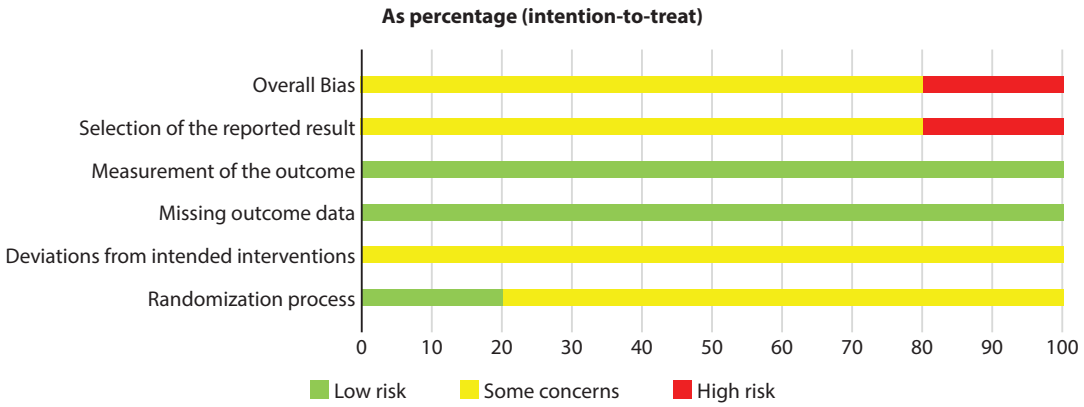


Figure E2. Summarized proportions for each domain of version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2)

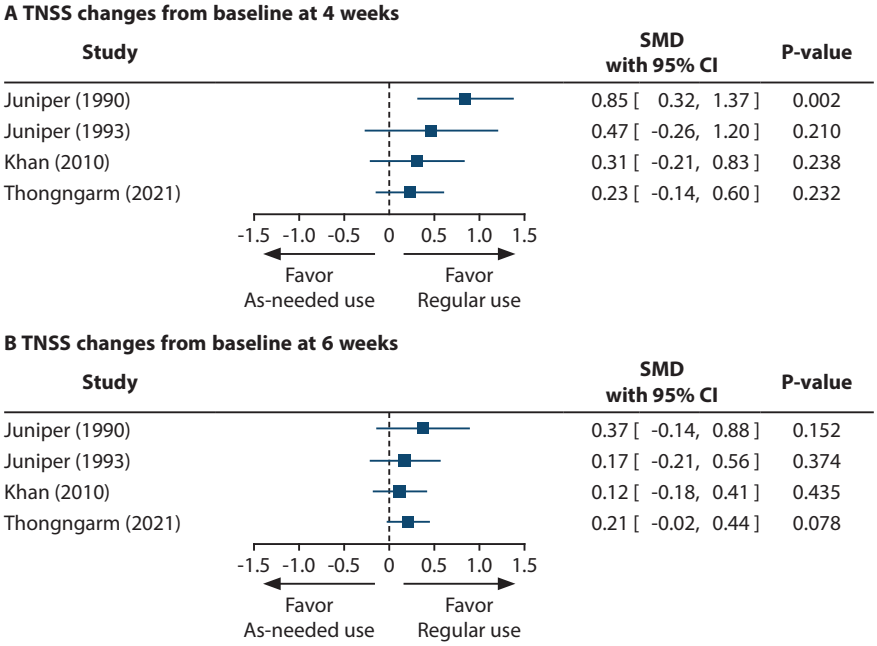


Figure E3. Cumulative meta-analysis results for the total nasal symptom score changes from baseline at 4 and 6 weeks of the included studies

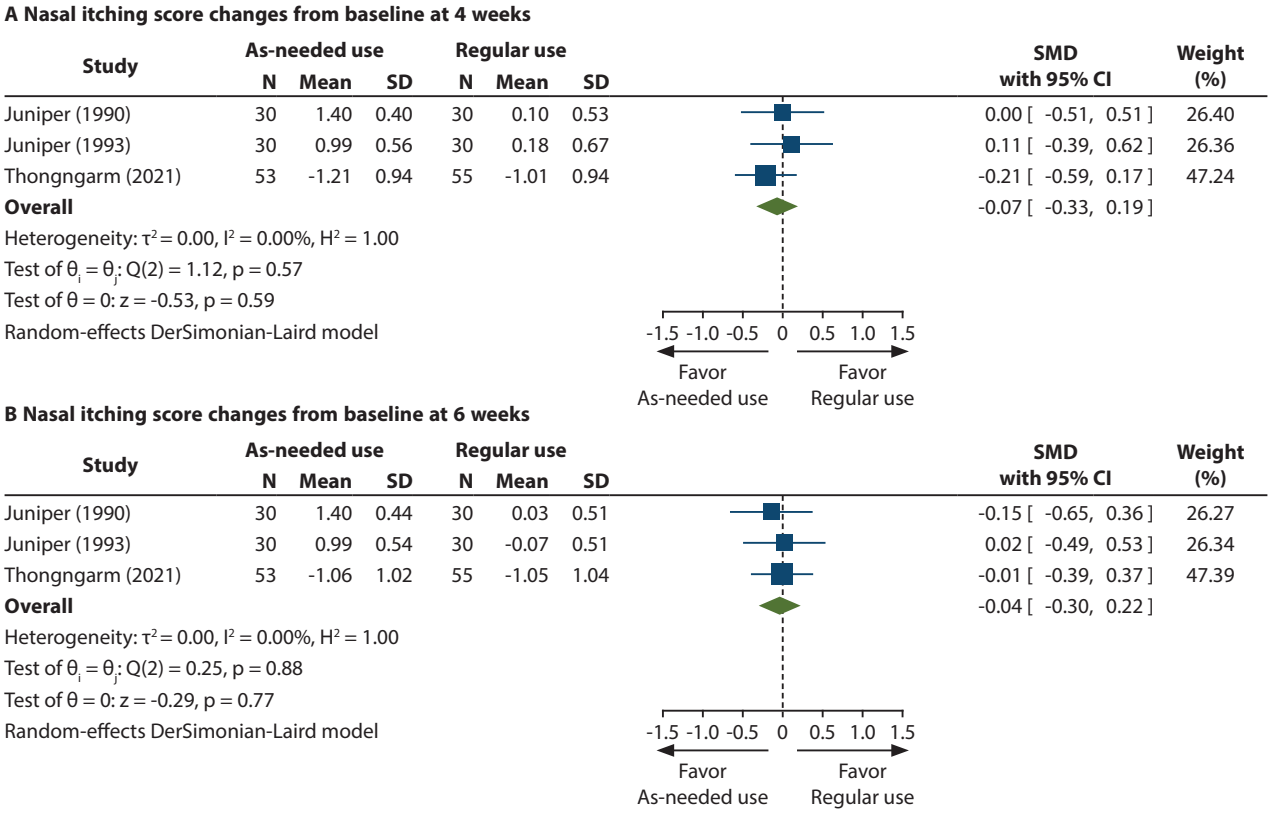
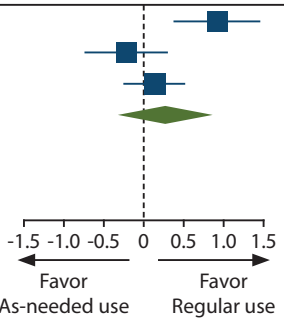


Figure E4. Nasal itching score changes from baseline at 4 and 6 weeks of the included studies

A Sneezing score changes from baseline at 4 weeks

Study	As-needed use N	Mean	SD	Regular use N	Mean	SD	SMD with 95% CI	Weight (%)
Juniper (1990)	30	1.40	0.40	30	0.16	0.45	0.92 [0.38, 1.45]	31.59
Juniper (1993)	30	0.99	0.50	30	0.33	0.58	-0.22 [-0.73, 0.29]	32.32
Thongngarm (2021)	53	-0.87	0.96	55	-1.00	1.00	0.13 [-0.25, 0.51]	36.09
Overall							0.27 [-0.33, 0.86]	

Heterogeneity: $\tau^2 = 0.22$, $I^2 = 79.35\%$, $H^2 = 4.84$
Test of $\theta_i = \theta_j$: Q(2) = 9.69, p = 0.01
Test of $\theta = 0$: z = 0.87, p = 0.38
Random-effects DerSimonian-Laird model



B Sneezing score changes from baseline at 6 weeks

Study	As-needed use N	Mean	SD	Regular use N	Mean	SD	SMD with 95% CI	Weight (%)
Juniper (1990)	30	1.40	0.49	30	0.02	0.38	0.59 [0.08, 1.11]	28.41
Juniper (1993)	30	0.99	0.35	30	-0.14	0.49	0.02 [-0.48, 0.53]	29.30
Thongngarm (2021)	53	-0.58	1.03	55	-1.10	1.05	0.50 [0.12, 0.88]	42.29
Overall							0.39 [0.06, 0.71]	

Heterogeneity: $\tau^2 = 0.03$, $I^2 = 31.54\%$, $H^2 = 1.46$
Test of $\theta_i = \theta_j$: Q(2) = 2.92, p = 0.23
Test of $\theta = 0$: z = 2.35, p = 0.02
Random-effects DerSimonian-Laird model

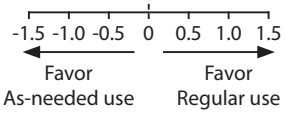
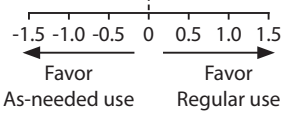


Figure E5. Sneezing score changes from baseline at 4 and 6 weeks of the included studies

A Rhinorrhea score changes from baseline at 4 weeks

Study	As-needed use N	Mean	SD	Regular use N	Mean	SD	SMD with 95% CI	Weight (%)
Juniper (1990)	30	1.40	0.43	30	0.23	0.57	0.32 [-0.19, 0.83]	26.11
Juniper (1993)	30	0.99	0.60	30	0.25	0.64	0.15 [-0.36, 0.65]	26.37
Thongngarm (2021)	53	-0.94	0.98	55	-1.02	1.00	0.08 [-0.30, 0.46]	47.53
Overall							0.16 [-0.10, 0.42]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: Q(2) = 0.54, p = 0.76
Test of $\theta = 0$: z = 1.20, p = 0.23
Random-effects DerSimonian-Laird model



B Rhinorrhea score changes from baseline at 6 weeks

Study	As-needed use N	Mean	SD	Regular use N	Mean	SD	SMD with 95% CI	Weight (%)
Juniper (1990)	30	1.40	0.45	30	0.07	0.47	0.09 [-0.42, 0.59]	26.44
Juniper (1993)	30	0.99	0.49	30	-0.03	0.49	-0.16 [-0.67, 0.34]	26.37
Thongngarm (2021)	53	-0.67	1.11	55	-0.97	1.13	0.27 [-0.11, 0.65]	47.19
Overall							0.11 [-0.15, 0.37]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: Q(2) = 1.79, p = 0.41
Test of $\theta = 0$: z = 0.80, p = 0.42
Random-effects DerSimonian-Laird model

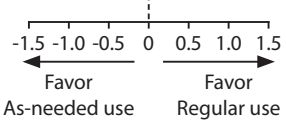


Figure E6. Rhinorrhea score changes from baseline at 4 and 6 weeks of the included studies

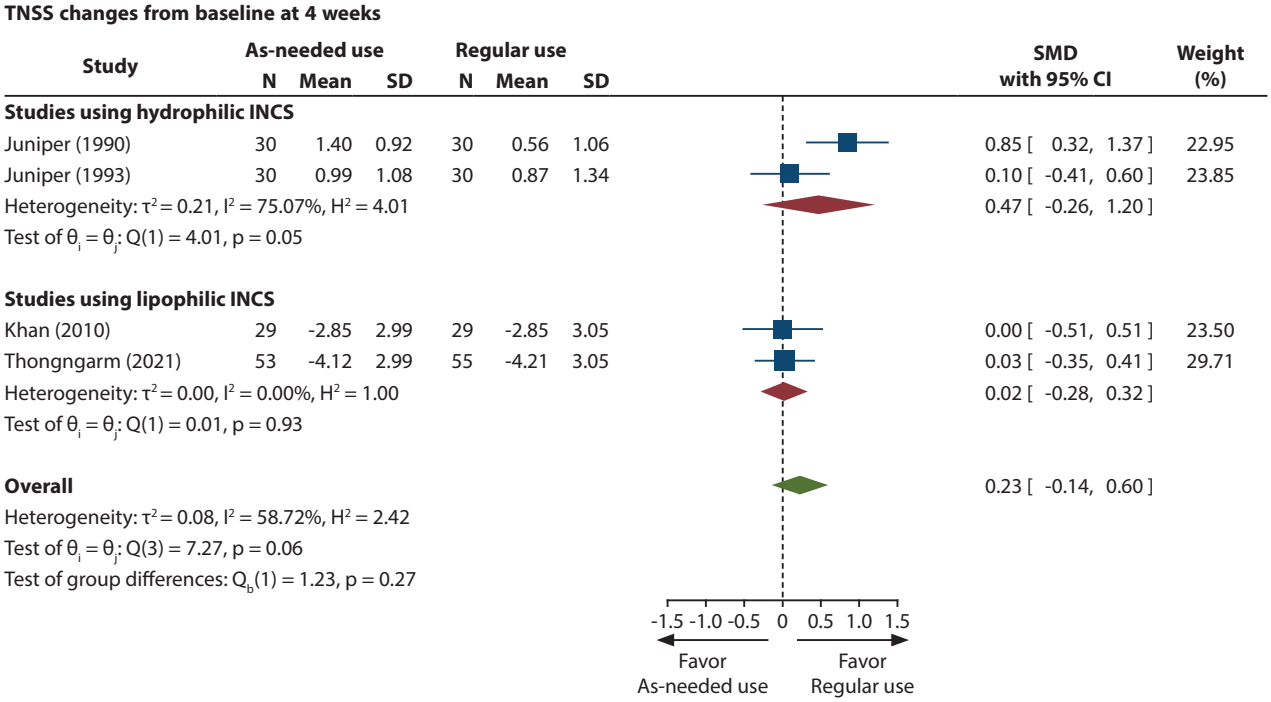


Figure E7. Subgroup analysis forest plot showing the efficacy of as-needed intranasal corticosteroid (INCS) compared to regular INCS in total nasal symptom score changes from baseline at 4 weeks by type of INCS (i.e., hydrophilic INCS or lipophilic INCS)

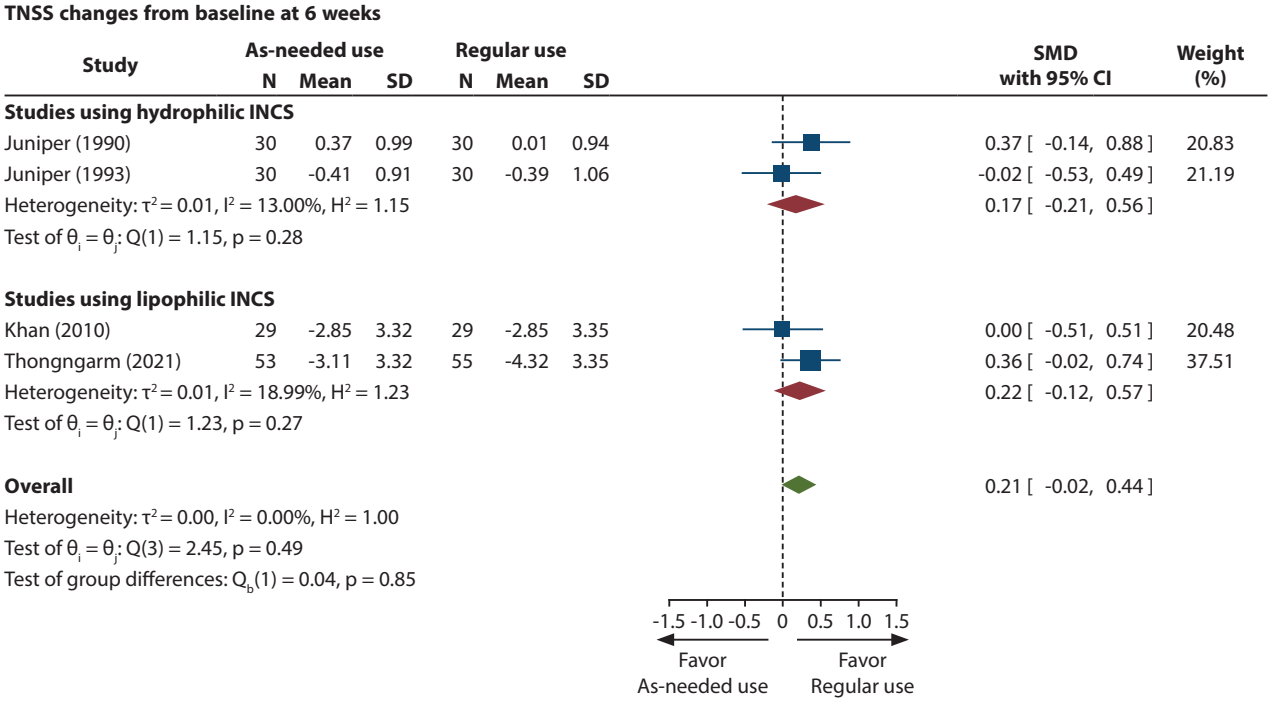


Figure E8. Subgroup analysis forest plot showing the efficacy of as-needed intranasal corticosteroid (INCS) compared to regular INCS in total nasal symptom score changes from baseline at 6 weeks by type of INCS (i.e., hydrophilic INCS or lipophilic INCS)

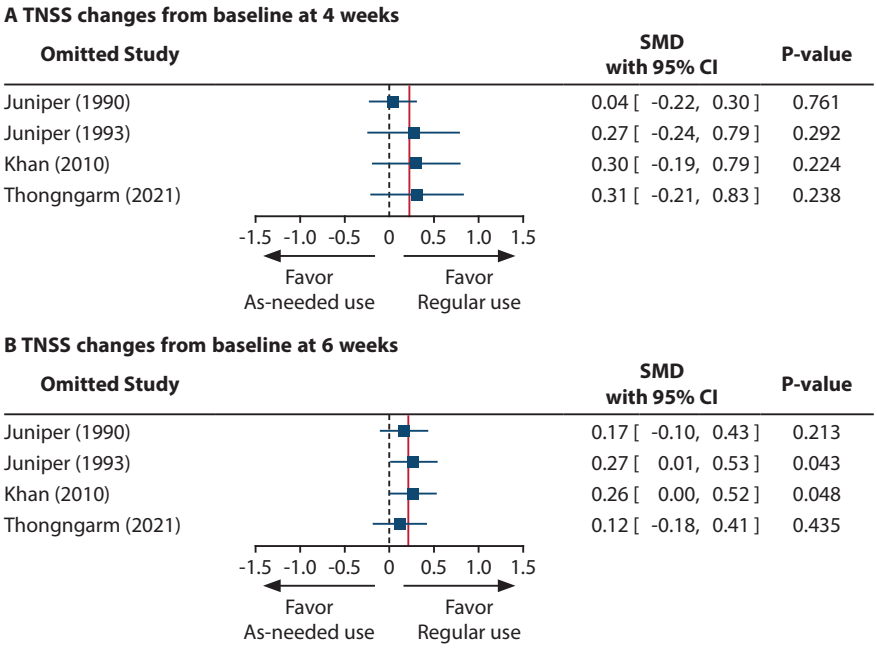


Figure E9. A leave-one-out sensitivity analysis on total nasal symptom score changes from baseline at 4 and 6 weeks of the included studies