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Original article

The efficacy and safety of H1-antihistamine versus Montelukast for allergic rhinitis: A systematic review and meta-analysis



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ABSTRACT

Purpose: In order to verify the differences of effectiveness and safety between SAHs and Montelukast, and to find out potential uncared-for problems, we performed a systematic review and Meta-analysis to proceed a qualitative describe and quantitative assessment.

Methods: We searched the databases of Pubmed, the Cochrane Library, Nature and Science as well as Wanfang data and CNKI from 2000 to March 2016, using key words “Montelukast SAH” or “H1-antihistamine Montelukast”, or “Loratadine Montelukast”, or “Desloratadine Montelukast”, or “Levocetirizine Montelukast”, or “Cetirizine Montelukast”, or “Fexofenadine Montelukast”. And also we included studies through relevant citations in related literature. Meta-analysis and bias of risk were performed. We analyzed Heterogeneity and publish bias as well.

Result: Montelukast seems more effective in nighttime symptoms compare with SAHs ($P=0.008$, $MD=-0.04$, $95\%CI: -0.08, -0.01$). No significant difference was found between Montelukast and SAHs in CSS ($P=0.10$, $MD=0.03$, $95\%CI: -0.01, 0.07$). Montelukast and SAHs combined therapy was more effective than Montelukast DNSS ($P=0.0006$, $MD=0.15$, $95\%CI: 0.07, 0.24$) but not in CSS ($P=0.04$, $MD=0.08$, $95\%CI: 0.00, 0.15$; Bonferroni correction $\alpha=0.017$).

Conclusion: Montelukast has a significant influence in improving patients' nasal symptoms quality of live but is not as effective as SAHs, and may have a slight advantage over SAHs in relieving nighttime symptoms significantly. Combined therapy is more effective in improving patients' day time symptom than Montelukast. Probably, patients might have a lower asthenia incidence rate when using Montelukas.

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1. Introduction

Allergic Rhinitis (AR) is a global disease. As former scientists defined, AR is induced by immunoglobulin E (IgE) mediated inflammation of the nasal membranes in response to allergen exposure [1]. Traditionally, it has been derived into Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis (PAR). People with SAR usually appear symptomatic during a specific season in which aeroallergens are present in the outdoor air such as tree and grass pollen in spring and summer and weed pollen in autumn; people with PAR are year-round sensitive to specific aeroallergens and usually are triggered by dust mite, animal dander, indoor molds and cockroaches [2]. AR symptoms are mainly nasal symptoms, like rhinorrhea, itching, and sneezing as well as eye signs, like redness and itching [3]. Actually, AR not only causes

patients physical discomforts but also influences their quality of life (QoL) [4]. In children and youths, suffering from AR may impact study efficiency, and in adults work ability [5].

Montelukast is a Leukotriene Receptor Antagonist (LTRAs). Leukotrienes (LTs) is generated by the metabolism of arachidonic acid via the 5-lipoxygenase (5-LO) pathway, which is involved in the rapid initial inflammation response [6,7]. LTRAs block the cysteinyl leukotriene receptor, i.e. LTC₄, LTD₄, and LTE₄, which are peptide-conjugated lipids produced by activated basophils, eosinophils, mast cells and macrophages, to relieve the symptom of AR [8,9]. Both leukotrienes and histamine are generated during nasal allergic reactions [5]. Cumulative clinical and laboratory evidence indicates that histamine plays a cardinal role as a chemical messenger in physiologic responses, neurotransmission, allergic inflammation, and immunomodulation by way of the H1-receptor. Most H1-antihistamines (H1-receptor antagonists, SAHs) are useful in treating these symptoms by possess the similar position [10–12].

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Both SAHs and LTRAs are applied widely as pharmaceuticals for the treatment of allergic rhinitis. However, Clinical Practice Guideline: Allergic Rhinitis published in 2015 [13] clearly pointed out that “Clinicians should not offer LTRAs as primary therapy for patients with AR”, one of the reasons being that it may be only be beneficial to a subset of patients. Further investigation still needs to be done because previous studies pointed out that Montelukast is effective and has a favorable safety profile in AR patients [14]. Three different Meta-analyses also gave out controversial outcomes. Grainger et al. [15] mentioned that Montelukast has an effect on reducing AR symptoms but to a lesser degree than antihistamines. Yu Xu et al. [9] pointed that SAHs and LTRAs have similar effects and safety, but LTRAs is superior for night time symptom relief. Juan Xiao et al. [16] found that Montelukast is effective but less so than other treatments. In order to verify the differences of effectiveness and safety between SAHs and Montelukast, we conducted a Meta-analysis to provide a qualitative description and quantitative assessment. Besides we intended to investigate the effects of Montelukast on nonasthmatic AR patients.

2. Methods

2.1. Study searching

We searched the databases of Pubmed, the Cochrane Library, Nature and Science as well as Wanfang data and China National Knowledge Infrastructure (CNKI) from 2000 to March 2016, using key words “Montelukast SAH” or “H1-antihistamine Montelukast”, or “Loratadine Montelukast”, or “Desloratadine Montelukast”, or “Levocetirizine Montelukast”, or “Cetirizine Montelukast”, or “Fexofenadine Montelukast”. And we also included studies through relevant citations in related literature.

2.2. Inclusion and exclusion criteria

Studies were included in our analysis if they met the following inclusion criteria: 1) randomised controlled trial (RCT) design; 2) patients with SAR or PAR. 3) with specific endpoint evaluation standards; 4) provision of efficacy or safety information; 5) comparing SAHs with Montelukast or placebo, or Montelukast with placebo or combination therapy; 6) data present as mean $\pm$ standard deviation (mean $\pm$ SD) or data to estimate them. Studies were excluded: 1) if reviews, systematic reviews or Meta-analysis; 2) if duplicate reports or reports on same subjects; 3) if providing insufficient data; 4) if focused on patient with asthma; 5) if combined therapy contained interventions other than SAHs and Montelukast.

2.3. Data extraction quality assessment

First author, publication year, sample size, AR type, country of birth, interventions, dose, mean age, gender, treatment duration and endpoint data were extracted by two independent investigators. Any inconformity solved by consensus. Endpoint indicators were determined by assessing the most common used scales from data characteristic. Risk of bias was assessed according to the Cochrane Collaboration's tool. We decided to drop studies with a high risk of bias.

2.4. Endpoints

After analyze data characteristic, composite symptoms score (CSS), daytime nasal symptoms score (DNSS), nighttime symptoms score (NSS), daytime eye symptoms score (DES) and rhinoconjunctivitis quality of life questionnaire (RQLQ) were widely

provided by original articles thus the data of them were pooled. And we combined separately as Montelukast vs. placebo, Montelukast vs. SAHs and Montelukast vs. combined therapy if there were more than 2 reports available.

2.5. Statistical analysis

Traditional Meta-analysis and bias risk assessment were performed using Review Manager 5.3 (RevMan 5.3). We pooled mean and SD. When original data provided 95% confidence interval (95% CI) we used a specific formula to estimate SD [17]. Heterogeneity analysis was performed and I^2 statistic was used to express the degree of heterogeneity. When $I^2 < 50\%$, we used a fixed effects model, otherwise a random effects model was used. A network meta-analysis was performed using R 3.2.4 (Ref). Network Meta-analysis can use indirect comparisons of treatments from RCTs to analyze and verify uncertain or uncared-for problems [18,19]. Thus we used a network Meta-analysis to investigate the differences between indirect comparisons between articles. *Totresdev*, *pD* and *DIC* were effect sizes that reflect sensitivity of network model. If they were close between fixed and random models, we considered the network model to be stable. Bonferroni correction was performed to adjust the results of multiple comparisons and 3 subgroup comparisons were made in each endpoint outcome combination thus the significance level $\alpha = 0.05/3$ (0.017). Outcomes were presented as mean difference (MD) and 95%CI. When the MD was negative and $P < 0.017$, Montelukast is more effective than the comparator. Accordingly, when $P < 0.017$ and MD was positive then the comparator is more effective than Montelukast. Whatever MD was if $P \geq 0.017$, there's no significant difference. Egger's test was used to evaluate the publication bias. Egger's test was performed by Stata 12.0.

3. Results

3.1. Article selection

A set of 211 articles was gathered to the key words. And after searching for the relevant citations; we obtained 22 related articles. We dropped the irrelevant reports through reading title and abstract. And also articles met exclusion criteria were excluded. 2 articles were excluded because of high risk of bias. In the end; we obtained 20 articles into qualitative description and quantitative analysis. 15 [20–34] articles were pooled into the traditional Meta-analysis and network Meta-analysis to evaluate the efficacy. 14 (7 articles in are same articles in efficacy analysis [20,25–30] and 7 articles are outside of efficacy analysis articles with safety information [35–41]) were obtained to assess the safety. Details present in Fig. 1. Articles characteristics are presented in Table 1 for efficacy and Table 2 for safety.

3.2. Risk of bias evaluation

We used the Cochrane Collaboration's tool to evaluate the risk of bias as is shown in Fig. 2. Two articles (A.M. Wilson 2002 [42] and A. M. Wilson 2001 [43]) with high risk in blinding of participants and personnel (performance bias) would be excluded from full model combination in Meta-analysis.

3.3. Result of efficacy

3.3.1. Montelukast vs. placebo

There were significant differences between Montelukast and placebo in CSS, DNSS, DES, NSS and RQLQ (Figs. 1–7, Table 3), which indicated that Montelukast is more efficacy than placebo.

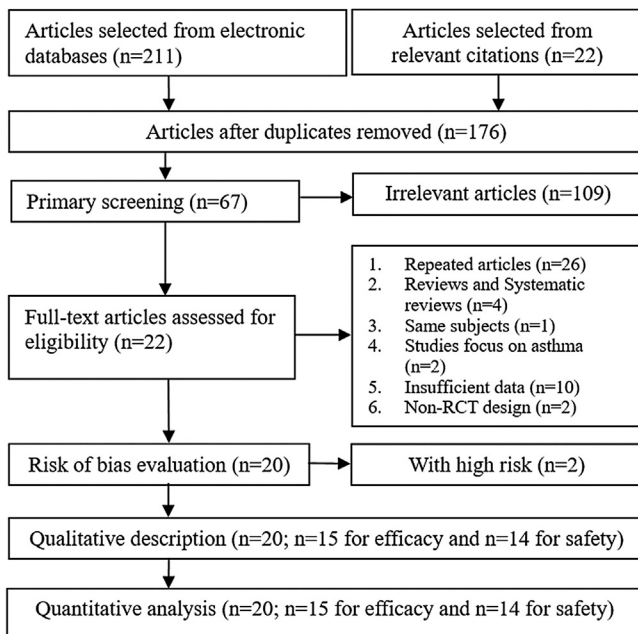


Fig. 1. Article screening technological process.

3.3.2. Montelukast vs. SHAs

There were significant differences between Montelukast vs. SHAs in DNSS (MD = 0.09, 95%CI: 0.05, 0.12, $P < 0.0001$; Fig. 8, Table 3), DES (MD = 0.06, 95%CI: 0.02, 0.10, $P = 0.002$; Fig. 9, Table 3), NSS (MD = -0.04, 95%CI: -0.08, -0.01, $P = 0.008$; Fig. 10, Table 3) and RQLQ (MD = 0.09, 95%CI: 0.02, 0.15, $P = 0.009$; Fig. 11, Table 3). These results indicate that, SHAs are more influential in patients' daytime nasal symptom and eye symptom, and could improve patient' QoL more effectively. However as to nighttime symptoms, Montelukast seems more effective. Comparing the composite symptoms (CSS) effect, they have no significant difference (MD = 0.03, 95%CI: -0.01, 0.07, $P = 0.10$; Fig. 12, Table 3).

3.3.3. Montelukast vs. combined therapy

As is shown in Fig. 13, Montelukast plus SAH is more effective than Montelukast alone in DNSS (MD = 0.15, 95%CI: 0.07, 0.24, $P = 0.0006$, Table 3). However, there's no significant difference in CSS (MD = 0.08, 95%CI: 0.00, 0.15, $P = 0.04$, Fig. 14, Table 3; Bonferroni correction $\alpha = 0.017$).

3.4. Network meta-analysis

Montelukast compare with Desloratadine was not added into direct comparison thus we used the indirect data to performed a Network meta-analysis intended to investigate the difference among Montelukast and Desloratadine based on data of RQLQ (the study Fexofenadine was not included into direct comparison either but it was not sufficient enough to perform to work out a reliable outcome through Network Meta-analysis). Network diagram was presented in Fig. 15. The Combined Montelukast vs. Desloratadine were: MD = 0.365, 95%CI: -0.1645 to 0.884 and there was no statistical significant difference. Sensitivity analysis of model were: Totresdev = 17.34, $pD = 17.1$ and DIC = 67.5 in the random effect model and totresdev = 16.67, $pD = 16.1$ and DIC = 65.8 in the fixed effect model. The three statistical indicators were close among fixed and random models, which showed that the network model was reliable.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
A. M. Wilson2001	+	+	-	?	+	+	+
A. M. Wilson2002	+	+	-	?	?	+	+
A. Pradalier2007	+	?	+	+	?	+	+
Anjuli S. Nayak2002	+	+	+	+	+	+	+
C. Bachert2009	+	+	+	+	+	+	+
Eli O. Meltzer2000	+	+	+	+	+	+	+
G. Philip2002	+	?	+	+	+	+	+
J. Van. Adelsberg2003	+	?	+	+	+	+	+
Janet Van Adelsberg2003	+	?	+	+	+	+	+
Jean Bousquel2010	+	+	+	+	+	+	+
K. Holmberg2009	+	+	+	+	+	+	+
Lee C-F2009	+	?	+	+	?	+	+
M. Ciebiada2008	+	?	+	+	?	+	+
M. J Noonan2002	+	?	+	+	+	+	+
P. Van Cauwenberge2000	+	?	+	+	+	+	+
Pascal Demoly2009	+	?	+	+	+	+	+
Piyush Patel2005	+	+	+	+	+	+	+
Susan Lu Pharm2009	+	+	+	+	+	+	+

Fig. 2. Risk of bias summary.

3.5. Safety assessment

We studied the side effect rate of Montelukast and SHAs, and we found that studies provided lower incidence rate of Asthenia and Headache of Montelukast than SHAs and many studies reported the incidence rate of somnolence of SHAs, but we didn't obtains

Table 1
Details for efficacy.

Author	Year	Country	Intervention (dose mg)	Week	N	Mean age	Gender (M/F)	Endpoints
Meltzer [20]	2000	US	Montelukast(10 mg)	2	95	33	40/55	CSS DNSS NSS DES
			Loratadine(10 mg)	2	92	34.5	43/49	CSS DNSS NSS DES
			Montelukast + Loratadine (10 + 10 mg)	2	187	33.75	83/104	CSS DNSS NSS DES
			Placebo	2	91	33	45/46	CSS DNSS NSS DES
Philip [21]	2002	Canada	Placebo	2	352	36	123/229	RQLQ
			Montelukast(10 mg)	2	348	37	115/233	CSS DNSS NSS DES RQLQ
			Loratadine(10 mg)	2	602	36	212/390	CSS DNSS NSS DES RQLQ
			Placebo	4	451	36	150/301	CSS DNSS NSS DES
Adelsberg [22]	2003	US	Montelukast(10 mg)	4	448	36	147/301	CSS DNSS NSS DES
			Loratadine(10 mg)	4	180	39	61/119	CSS DNSS NSS DES
			Placebo	2	566	36	183/383	CSS DNSS NSS DES RQLQ
			Montelukast(10 mg)	2	522	36	196/326	CSS DNSS NSS DES RQLQ
Van Adelsberg [23]	2003	US	Loratadine(10 mg)	2	171	35	71/100	CSS DNSS NSS DES RQLQ
			Placebo	2	57	35.1	36/21	CSS DNSS
			Montelukast(10 mg)	2	112	35.6	47/70	CSS DNSS
			Loratadine(10 mg)	2	116	34.8	41/75	CSS DNSS
Susan Lu [24]	2009	US	Placebo	2	53	33.6	37/17	CSS DNSS
			Montelukast(10 mg)	2	112	35.6	47/70	CSS DNSS
			Loratadine(10 mg)	2	116	34.8	41/75	CSS DNSS
			Montelukast + Loratadine (10 + 10 mg)	2	233	35.2	88/145	CSS DNSS
Susan Lu ^a	2009	US	Placebo	2	149	37	86/63	DNSS RQLQ
			Montelukast(10 mg)	2	155	37	102/53	CSS DNSS NSS DES RQLQ
			Loratadine(10 mg)	2	301	37	191/110	CSS DNSS NSS DES RQLQ
			Montelukast + Loratadine (10 + 10 mg)	2	302	38	208/94	CSS DNSS NSS DES RQLQ
Anjuli S. Nayak [25]	2002	US	Placebo	2	149	37	86/63	DNSS RQLQ
			Montelukast(10 mg)	2	155	37	102/53	CSS DNSS NSS DES RQLQ
			Loratadine(10 mg)	2	301	37	191/110	CSS DNSS NSS DES RQLQ
			Montelukast + Loratadine (10 + 10 mg)	2	302	38	208/94	CSS DNSS NSS DES RQLQ
Van Cauwenberge [26]	2000	US & Canada	Placebo	2	225	30.6	104/121	RQLQ
			Fexofenadine HCl	2	232	30.9	101/131	RQLQ
			Loratadine(10 mg)	2	228	31.9	101/127	RQLQ
			Placebo	2	416	33.6	269/157	DNSS NSS DES RQLQ
George Philip [27]	2004	US & Europe	Montelukast(10mg)	2	415	33	265/150	DNSS NSS DES RQLQ
			placebo	3	291	–	–	RQLQ
			Desloratadine(10 mg)	3	293	–	–	RQLQ
			Placebo	2	245	30.6	118/127	RQLQ
K. Holmberg [28]	2009	France& Sweden	Desloratadine(5 mg)	2	242	29.8	126/116	RQLQ
			Placebo	4	356	33.9	157/99	RQLQ
			Desloratadine(5 mg)	4	360	34	151/109	RQLQ
			Placebo	2	245	–	–	RQLQ
C. Bachert [29]	2009	Belguim	Desloratadine(5 mg)	2	242	29.8	126/116	RQLQ
			Placebo	4	356	33.9	157/99	RQLQ
			Desloratadine(5 mg)	4	360	34	151/109	RQLQ
			Placebo	2	245	–	–	RQLQ
Jean Bousquet [30]	2010	US	Desloratadine(5 mg)	2	242	–	–	RQLQ
			Placebo	2	249	32.4	129/120	RQLQ
			Desloratadine(5 mg)	2	234	32.7	121/113	RQLQ
			Placebo	2	990	36.6	358/632	DNSS NSS RQLQ
I Jáuregui [31]	2011	Spanish	Montelukast(10 mg)	2	1002	36.3	358/644	DNSS NSS RQLQ
			placebo	2	115	39.2	44/71	RQLQ
			Desloratadine(5 mg)	2	118	40.3	58/60	RQLQ
			Placebo	2	118	40.3	58/60	RQLQ

^a Article contains 2 different studies.**Table 2**
Details for safety.

Author	Year	Treatment	N	Withdrew rate ^a %	Asthenia%	Headache%	Somnolence%	Other [#] %
Van Cauwenberge [26]	2000	Fexofenadine	232	–	0.4	3	1.7	3.4
K. Holmberg [28]	2009	Desloratadine	293	–	9	3	–	0
Jean Bousquet [30]	2010	Desloratadine	301	–	1.9	1.1	2.2	1.1
George Philip [27]	2004	Montelukast	415	–	–	1	0	1.2
C. Bachert [29]	2009	Desloratadine	242	<1	1.2	11.2	3.7	0
Anjuli S. Nayak [25]	2002	Montelukast	155	<1	1	3	–	1
		Loratadine	301	<1	1	4	–	1
Carlos E. Baena-Cagnani [35]	2003	Desloratadine	311	–	–	3.5	–	0
		Montelukast	311	–	–	3.5	–	0
James H. Day [36]	2008	Montelukast	156	–	0.6	3.2	–	0
		Levocetirizine	157	–	1.3	0	1.3	0
Julius van Bavel [37]	2009	Azelastine	266	1.5	–	–	–	9
Shailen Shah [38]	2009	Azelastine 0.15%	177	–	–	0.6	1.7	11.7
		Azelastine 0.10%	169	–	–	1.8	0.6	13.5
Eli O. Meltzer [20]	2000	Montelukast	95	–	–	5.3	–	0
		Loratadine	92	–	–	8.7	–	0
David P. Skoner [39]	2014	Cetirizine	158	–	–	6.3	2.5	4.4
Joaquín Sastre [40]	2012	Cetirizine	214	–	0.9	5.1	6.9	6.5
S. Fantin [41]	2008	Cetirizine	174	–	–	29	8	9

^a Patients withdrew are drug relevant.[#] Other side effects contain diarrhoea, nausea, pharyngitis, dry mouth, Pruritus, rash, bitter tast, nasal discomfort, epistaxis, upper respiratory tract infection, nasal discomfort, abdominal pain, dyspepsia, nasopharyngitis, increased appetite, dizziness and pharyngolaryngeal pain.

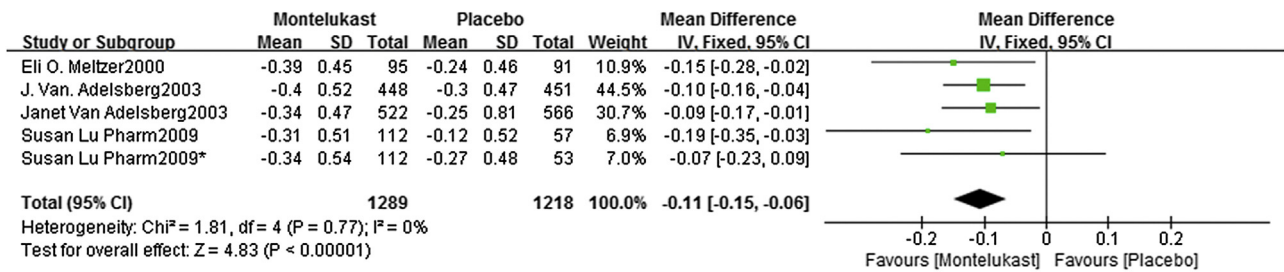


Fig. 3. Montelukast vs. placebo of CSS.

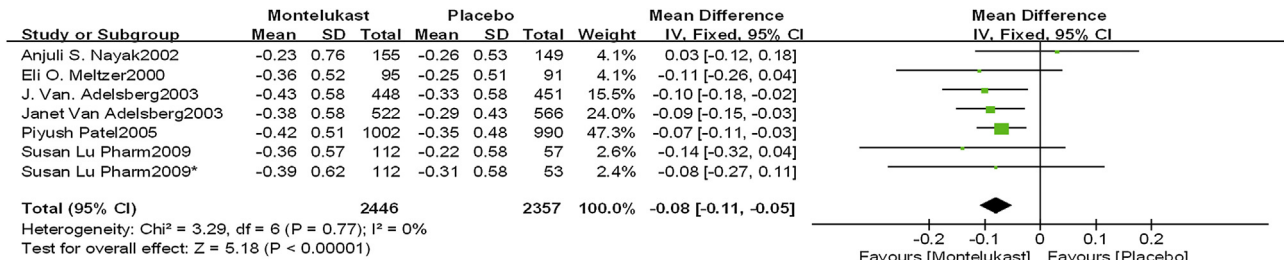


Fig. 4. Montelukast vs. placebo of DNSS.

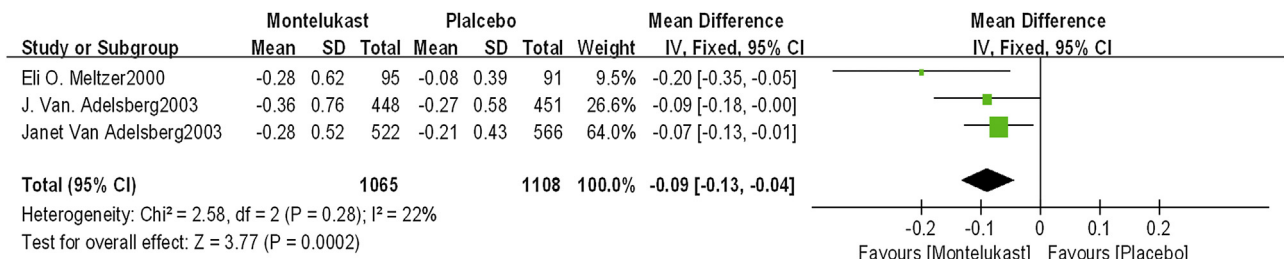


Fig. 5. Montelukast vs. placebo of DES.

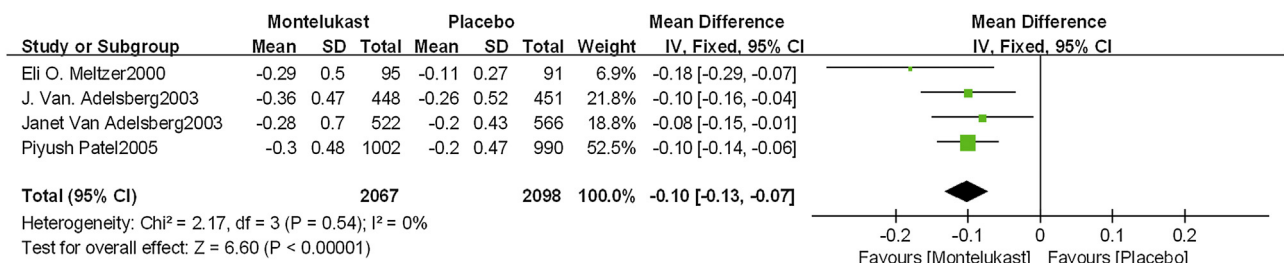


Fig. 6. Montelukast vs. placebo of NSS.

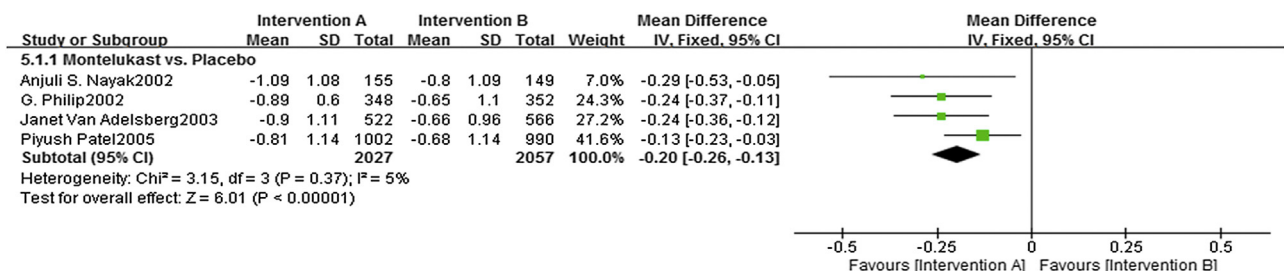
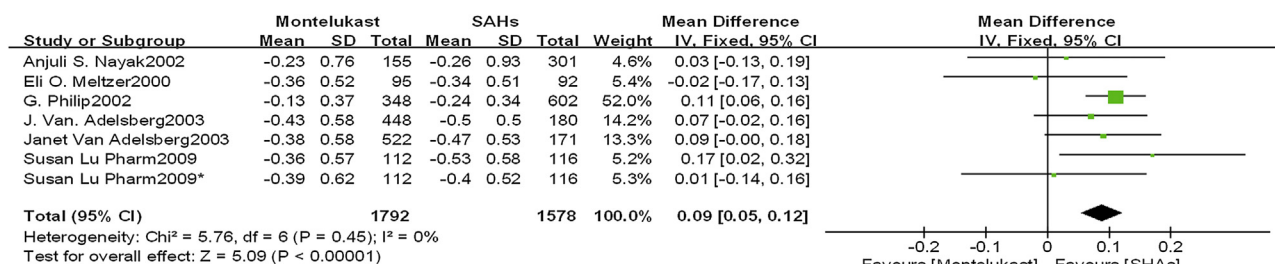
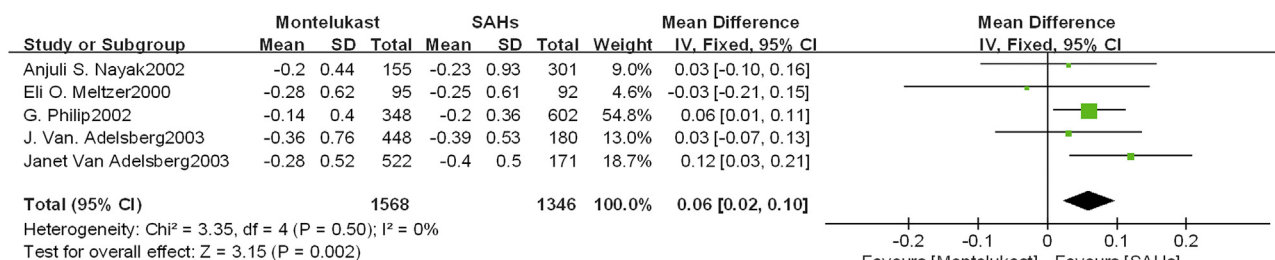
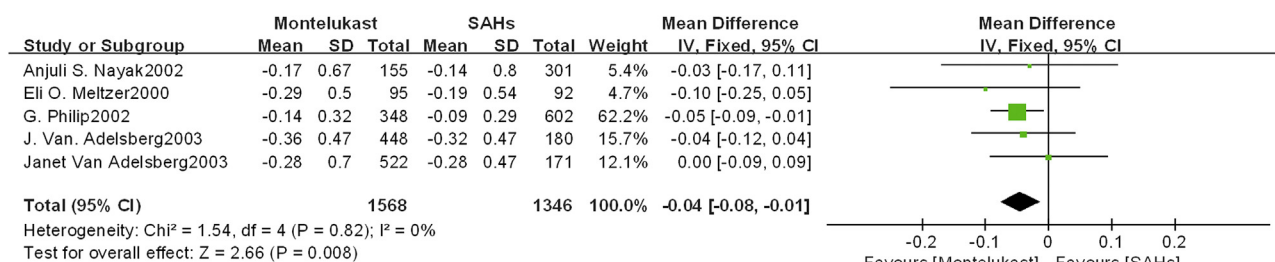


Fig. 7. Montelukast vs. placebo of RQLQ.

Table 3

List of Meta-analysis outcomes.

Comparison	Endpoint	MD	Lower 95%CI limit	Higher 95%CI limit	P	I ²
Placebo	CSS	-0.11	-0.23	-0.06	<0.00001	0%
	DNSS	-0.08	-0.11	-0.05	<0.00001	0%
	DES	-0.09	-0.13	-0.04	0.0002	22%
	NSS	-0.10	-0.13	-0.07	<0.00001	0%
	RQLQ	-0.20	-0.26	-0.13	<0.00001	5%
SAHs	CSS	-0.03	-0.01	0.07	0.10	0%
	DNSS	0.09	0.05	0.12	<0.00001	0%
	DES	0.06	0.02	0.10	0.002	0%
	NSS	-0.04	-0.08	-0.01	0.008	0%
	RQLQ	0.09	0.02	0.15	0.009	0%
Combine therapy	CSS	0.08	0.00	0.15	0.04	0%
	DNSS	0.15	0.07	0.24	0.0006	23%

**Fig. 8.** Montelukast vs. SAHs of CSS.**Fig. 9.** Montelukast vs. SAHs of DNSS.**Fig. 10.** Montelukast vs. SAHs of DES.

somnolence incidence rate of Montelukast (Table 2). We combined the rate of side effect and we found the incidence rate of Asthenia of SAHs and Montelukast were 2.25 (95%CI: 1.38, 3.12) and 0.75 (95%CI: 0.3, 1.2), the incidence rate of headache of SHAs and Montelukast were 3.57 (95%CI: 3.42, 3.72) and 2.67 (95%CI: 1.37, 3.98), respectively. And the incidence rate of somnolence of SHAs was 2.66 (95%CI: 1.80, 3.52) (Table 4).

3.6. Publication bias

We used Egger's test to assess publish bias and $P=0.484$ thus there's no publish bias.

4. Discussion

Our study aimed at assessing the efficacy of montelukast in AR patients based on high quality studies. We used strict inclusion

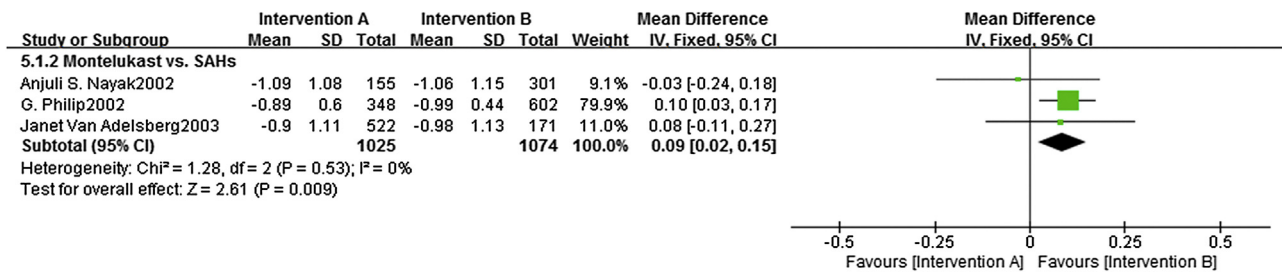


Fig. 11. Montelukast vs. SAHs of NSS.

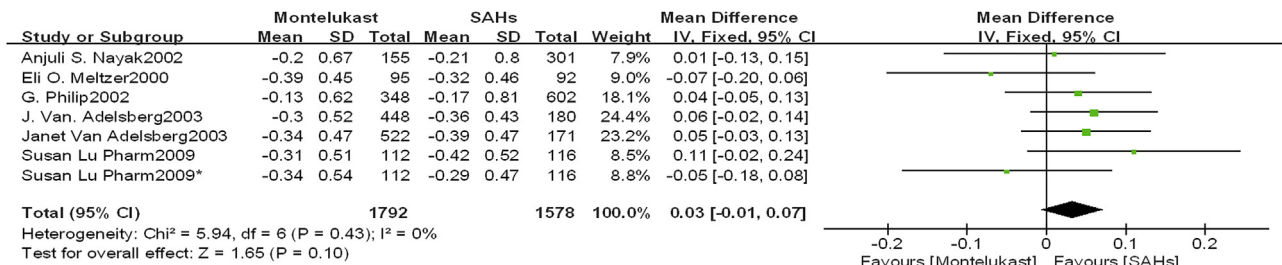


Fig. 12. Montelukast vs. SAHs of RQLQ.

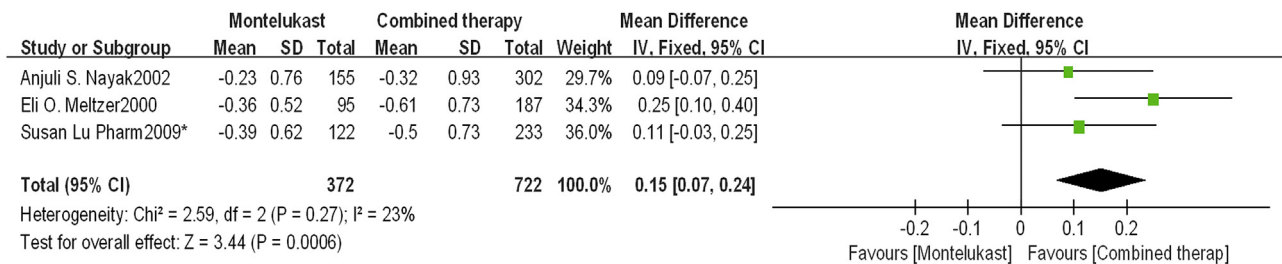


Fig. 13. Montelukast vs. Combined therapy of CSS.

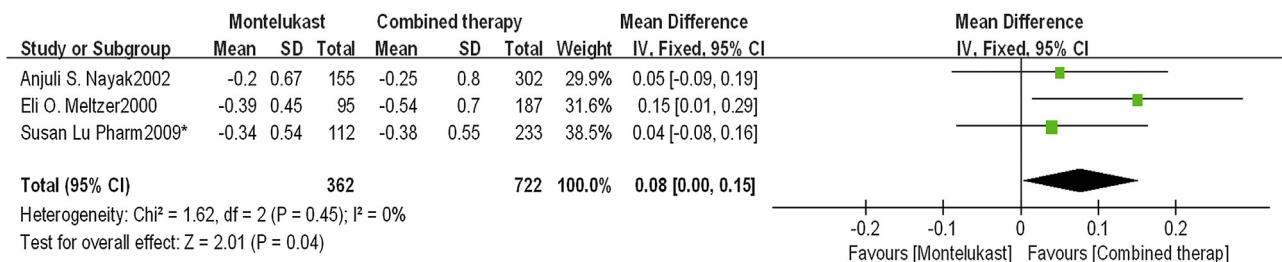


Fig. 14. Montelukast vs. Combined therapy of DNSS.

and exclusion criteria for studies and performed a thorough quality evaluation.

Our approach combined traditional and network meta-analysis to more precisely investigate the differences between montelukast and SAHs. A majority of studies dealt with montelukast and loratadine. Our analysis provides some confirmation that loratadine are more effective than montelukast in improving patients' daytime nasal symptoms, daytime eye symptoms score (DES) and QoL. However, Montelukast is more effective in improving patients' nighttime nasal symptoms which is in line with that of Yu Xu et al. [9] who reported that montelukast is more effective in improving nighttime symptoms in non-asthma patients. RQLQ is a more comprehensive index which accounts not only for nasal

symptoms but also for eye symptoms, asthenia etc [44]. Thus the network part used RQLQ as the indicator to compare Montelukast and Desloratadine and we found that there's might no significant difference among Montelukast and Desloratadine in the improvement of patients' QoL.

We found that combined therapy with Montelukast is more effective than Montelukast in patients' daytime but not significant in composite nasal symptoms. Goh et al. [45]. in a randomised, double-blind, placebo-controlled study found that the combination of oral montelukast and Fluticasone propionate nasal spray improved symptoms of patients with moderate and severe AR. Ciebiada [46] as well as Cingi et al. [47] emphasize that montelukast combined with SAHs can improve QoL. Erdogan

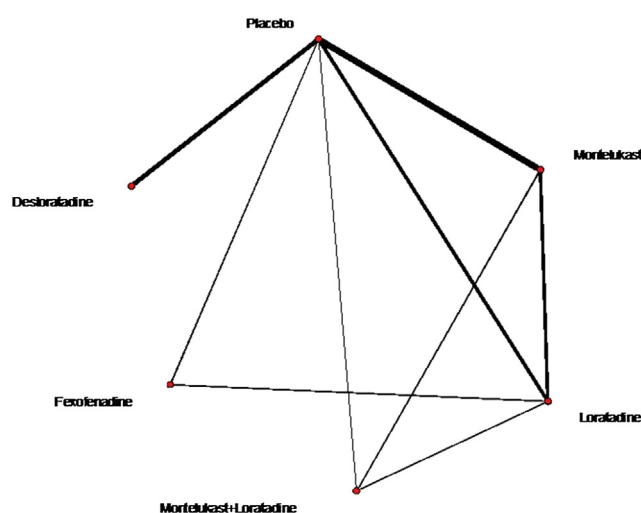


Fig. 15. Network of AR of RQLQ.

Table 4
Safety of Montelukast vs. SHAs.

	Asthenia/Fatigue Rate (95%CI)	Headache Rate (95%CI)	Somnolence Rate (95%CI)
SHAs	2.25(1.38,3.12)	3.57(3.42,3.72)	2.66(1.80,3.52)
Montelukast	0.75(0.3,1.2)	2.67(1.37,3.98)	–

[48] found desloratadine plus montelukast has a positive impact on quality of life, and sleep symptoms in particular which may reflect a specific effect of Montelukast at night.

AR leads to a significant economic burden. Kim [49] and Goodman [50] found Montelukast to cost more than SHAs. Which means even if they have similar efficacy in relieving patients' nasal symptom and improving patient's QoL, SHAs is a better choice when considering of the cost.

As to safety, the report rate of side effect of SHAs is more frequent than Montelukast. The pooled incidence rate of asthenia of SHAs and Montelukast were 2.25 (95%CI: 1.38, 3.12) and 0.75 (95%CI: 0.3, 1.2), the pooled incidence rate of headache of SHAs and Montelukast were 3.57 (95%CI: 3.42, 3.72) and 2.67 (95%CI: 1.37, 3.98), respectively. Especially of asthenia, the higher limit of 95%CI of Montelukast is lower than the lower limit of 95%CI of SHAs. Directly, from the combined data we may assume that Montelukast might has a lower incidence rate of asthenia. Probably, future studies could pay more attention on the direct comparison of safety between Montelukast and SHAs.

There are 3 limitations in our meta-analysis. First, although we tried our best to select articles, some articles, especially those that are not written in English cannot be obtained. Second, network meta-analysis can reveal undetected results but it may produce bias. For example, the effects estimated may be biased when indirect comparisons are based on low-quality trials [19]. Third, this analysis didn't incorporate all the risk factors such as age, ethnicity, and disease duration. The risk factors have to be weighed against the benefits of these treatment regimens.

5. Conclusion

Montelukast has a significant influence in improving patients' nasal symptoms quality of life but is not as effective as SHAs, and may have a slight advantage over SHAs in relieving nighttime symptoms significantly. Combined therapy is more effective in improving patients' day time symptom than Montelukast.

Probably, patients might have a lower asthenia incidence rate when using Montelukast.

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