Bilastine association with lower risk of adverse events. A systematic review and meta-analysis of randomized clinical trials.

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Abstract

OBJECTIVES: Bilastine is a new second-generation H1 antagonist recently approved in 28 countries of the European Union for the management of allergy symptoms. We systematically evaluated symptom scores and adverse event with the use of bilastine.

METHODS: We searched PubMed and ClinicalTrials.gov for randomized, double-blind, placebo-controlled trials of bilastine that reported on total symptom scores and the number of adverse events as study outcomes. A random-effects model using the maximum-likelihood estimator was used to evaluate the effects of bilastine on symptom scores and adverse events. We measured effect sizes as standardized mean differences and expressed associations as relative risk (RRs) ratios and their 95% CIs.

RESULTS: Three trials were selected (n=1914), including two studies of seasonal allergic rhinitis, and one study of chronic idiopathic urticaria. Control arms included desloratadine, cetirizine, levocetirizine, and placebo. The standardized mean difference of symptom scores was significantly lower in the bilastine group when compared to placebo (SMD -0.45; 95% CI -0.56 to -0.34; $p<0.0001$). The standardized mean difference of symptom scores was not significantly different in the bilastine vs. other H1 blockers comparison (SMD -0.07; 95% CI: -0.18 to -0.04; p=0.21). Neither the I^2 statistic (0.00%) nor the test for heterogeneity (p=0.24) indicated significant variability in the observed outcomes. Bilastine compared to other H1 blockers had a significantly 16% lower relative risk of adverse events (RR = 0.84; 95% CI: 0.71 to 0.98; 0.03). Neither the I^2 statistic 1.02% nor the test for heterogeneity (p = 0.21) indicated significant variability in the observed outcomes.

CONCLUSIONS: Bilastine provides as effective treatment as other H1 blockers when compared to placebo, and is associated with significantly fewer adverse reactions than comparable treatments.

Introduction

Bilastine is a novel selective histamine H_1 receptor antagonist [1]. In animal studies, bilastine was shown to have antihistaminic and antiallergic properties similar to that of cetirizine and more potent than that of fexofenadine [2]. In clinical studies the optimal therapeutic dose for sustained H_1-blocking effects was observed at 20 mg once daily [3,4].

At the recommended dosage the drug is non-sedative, does not produce any driving impairment in doses up to 40 mg [5], and shows no clinically significant cardiotoxicity in doses up to 100mg [6]. Large clinical trials have demonstrated bilastine as safe and efficacious symptomatic treatment of chronic idiopathic urticaria [7], as well as seasonal [8,9] and perennial [10] allergic rhinitis. in 2010 bilastine was approved for use in the European Union [11], but is not yet available in the U.S. market.

Significance of the study

There are no other systematic reviews of bilastine treatment in the literature. Jáuregui et al. evaluated available trial data with a focus on quality of life [12], but did not perform a formal meta-analysis. This is the first systematic review and meta-analysis of bilastine randomized clinical trials.

Methods

Selection of studies

We searched ClinicalTrials.gov and PubMed for randomized, placebo-controlled clinical trials of bilastine (search term was *bilastine*). ClinicalTrials.gov query returned 13 studies, but no results were included with the studies. PubMed query returned 35 papers out of which 6 described studies that met the above-specified inclusion criteria and were assessed for eligibility [3,7–10,13]. An overview is provided in Table 1. After review three studies were included in the final meta-analysis encompassing 630 patients in the bilastine arm [7–9]. A diagram of study selection prepared according to the PRISMA statement [14] is shown in Figure 1.

Outcomes

All included trials assessed the severity of nasal and non-nasal symptoms on a predetermined scale to provide a total symptom score (TSS). The primary outcomes were area under the curve for the TSS over the entire treatment period or change in TSS AUC from baseline. The secondary outcome was the number of patients reporting more than one adverse event (AE) over the treatment period.

Extraction of information

TA extracted general characteristics of the studies (details of blinding and randomization, study populations, treatment type and duration), the number of patients per trial arm, and the outcome values. This information was reviewed by RP, and any discrepancies were resolved by agreement.

Study quality

The Jadad scale is a five-point scale evaluating the quality of randomized clinical trials [15]. One point is given if a study is described as randomized, one point if described as double blind, and one point for description of withdrawals. One additional point (two points total) can be added for adequate description of randomization and blinding. However, points can also be subtracted if the described method of randomization or blinding is inappropriate (two points total). A Jadad score of 4 or more was considered high quality.

Meta-analysis

The meta-analysis was performed using the metafor R package [16] and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. We used a random-effects model using the maximum-likelihood estimator. Our main measure of association was the standardized mean difference for primary outcomes (TSS

AUC or difference from) and the relative risk of patients reporting more than 1 adverse event during a trial (secondary outcome). Heterogeneity was evaluated using the Q test and quantified with the I^2 statistic. Publication bias was evaluated with Egger regression test for funnel plot asymmetry.

Results

The estimated standardized mean difference of symptom scores in bilastine treated vs. placebo group was equal to -0.45 (95% CI: -0.56 to -0.34) indicating that bilastine lowered symptom scores when compared to placebo. The null hypothesis could be clearly rejected ($z = -7.83$, $p<0.0001$). Neither the I2 statistic (% of total variability due to heterogeneity) nor the test for heterogeneity ($Q = 3.11$, $df = 2$, $p = 0.22$) indicated significant variability in the observed outcomes. A graphical overview of the results is shown in Figure 1.

The estimated standardized mean difference of symptom scores in bilastine treated vs. other H_1 blockers group was equal to -0.07 (95% CI: -0.18 to -0.04) indicating there was no difference in treatment effects. The null hypothesis could not be rejected ($z = -1.27$, $p = 0.21$). Neither the I^2 statistic 0.00% nor the test for heterogeneity ($Q = 2.88$, $df = 2$, $p = 0.24$) indicated significant variability in the observed outcomes. A graphical overview of the results is shown in Figure 2.

Comparing bilastine to other H_1blockers the estimated average log relative risk of adverse events (AE) was equal to -0.18 (95% CI: -0.34 to -0.02). For easier interpretation, we transformed these values back to the relative risk scale through exponentiation (i.e., RR = 0.84 with 95% CI: 0.71 to 0.98). The results therefore suggest that the risk of AE in the bilastine treated group was on average 16% smaller compared to treatments with other H_1blockers. The null hypothesis was rejected ($z = -2.14$, $p = 0.03$). Neither the I^2 statistic 1.02% nor the test for heterogeneity ($Q = 3.12$, $df = 2$, $p = 0.21$) indicated significant variability in the observed outcomes. A graphical overview of the results is shown in Figure 3.

No evidence of publication bias was found using regression tests (TSS bilastine vs. placebo $p = 0.12$; TSS bilastine vs. H_1 blocker $p = 0.13$; AE bilastine vs. H_1 blocker $p=0.53$). Script and datasets used in the analysis are available from figshare (http://dx.doi.org/10.6084/m9.figshare.658873).

Discussion

Out of 13 bliastine control trials registered at ClinicalTrials.gov, not a single one had posted results. This is not an uncommon practice, as current requirements of the International Committee of Medical Journal Editors do not go beyond the mandatory initial registration [17], effectively making the clinical trials registries unusable from the systematic review perspective. In particular, if studies with small or controversial findings remain unpublished,

meta-analysis may not always reflect clinical reality. Several statistical techniques have been developed to detect such bias [18], and the regression test for funnel plot asymmetry used here did not demonstrate any such bias.

One of the more interesting results of this analysis is the statistically significant moderately lower risk of adverse events in patients taking bilastine compared to other H_1 blockers. This effect was strongest in comparison with desloratadine and cetirizine, but was not present in in the Zuberbier et al. study comparing bilastine to levocetirizine [7]. In the absence of more trial data, we can only speculate whether this was due to this particular study having a mixed ethnic background (Europe and Argentina) in contrast to other two trials uniformly drawn from Europe or due to a different H_1 blocker that bilastine was compared against. It is worth noting however that another study with mixed background comparing bilastine to cetirizine in the treatment of perennial allergic rhinitis demonstrated a paradoxically high placebo response in South African subpopulation [10], which suggests there may be additional pharmacogenomics effects involved in non-European populations.

Conclusions

Bilastine provides as effective treatment as other H_1 blockers when compared to placebo, and is associated with significantly fewer adverse reactions than comparable treatments.

Tables and Illustrations

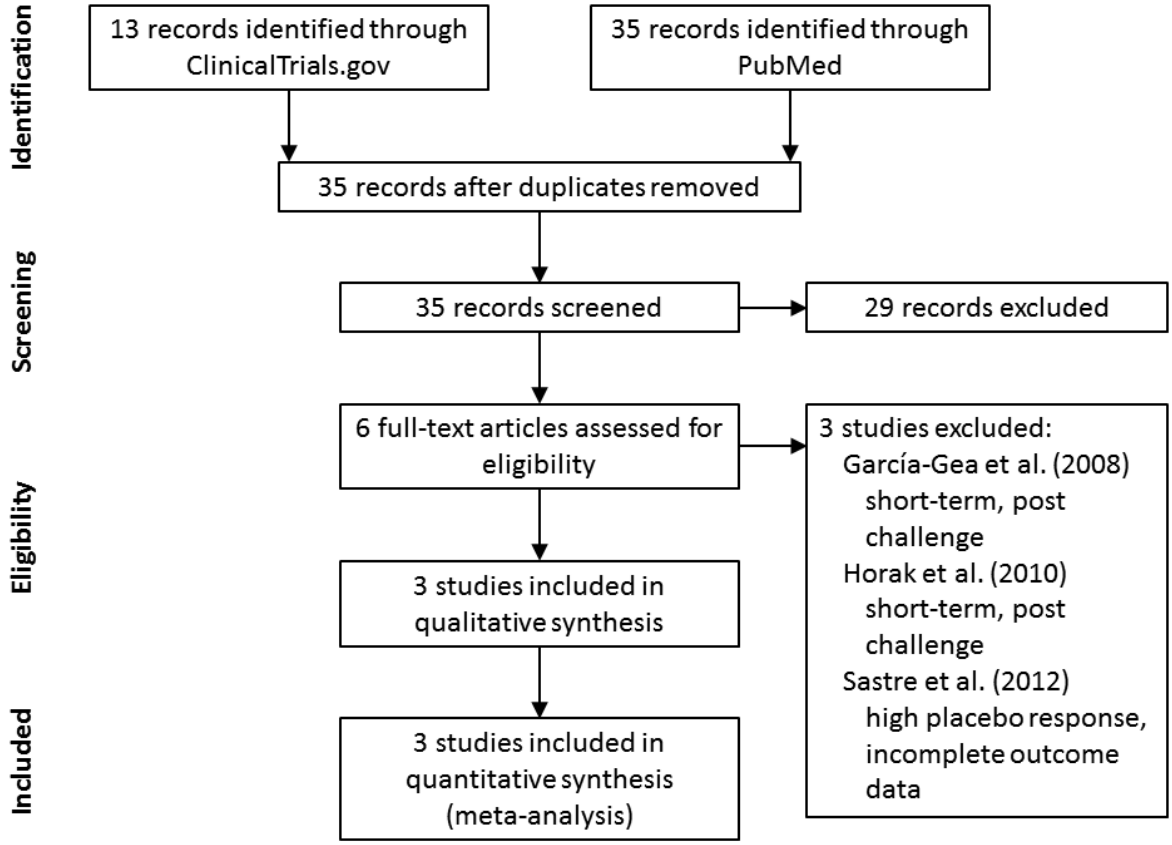

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow of information through different phases of systematic review.

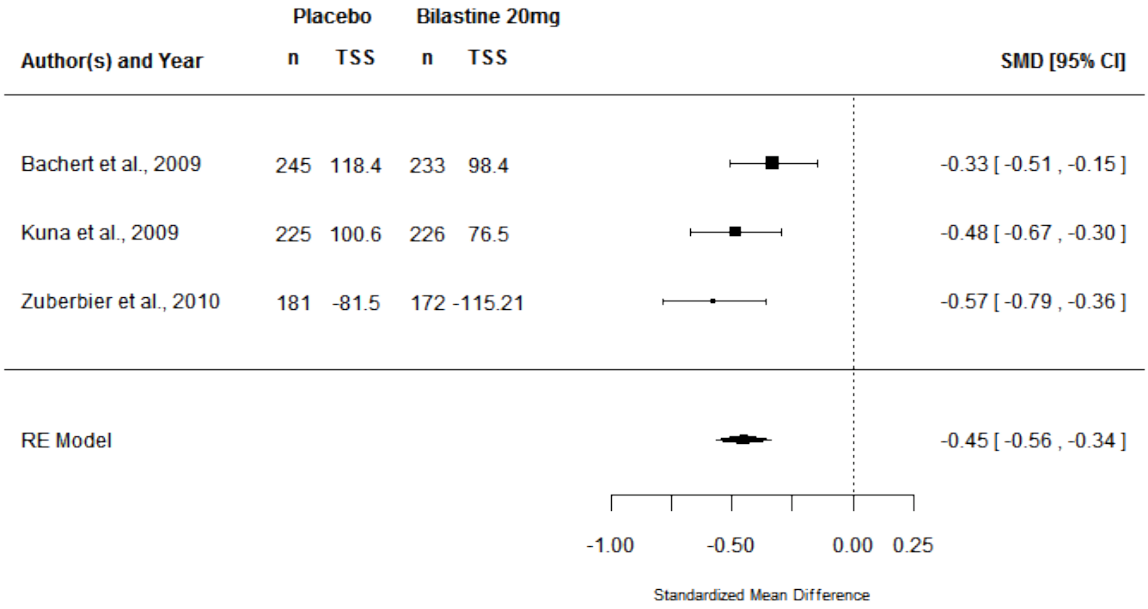

Figure 2. Forest plot showing the results of 3 studies examining the effectiveness of bilastine. The figure shows the standardized mean difference of total symptom scores (TSS) in the treated versus the control group with corresponding 95% confidence intervals in the individual studies and based on a random-effects model ($p < .0001$).

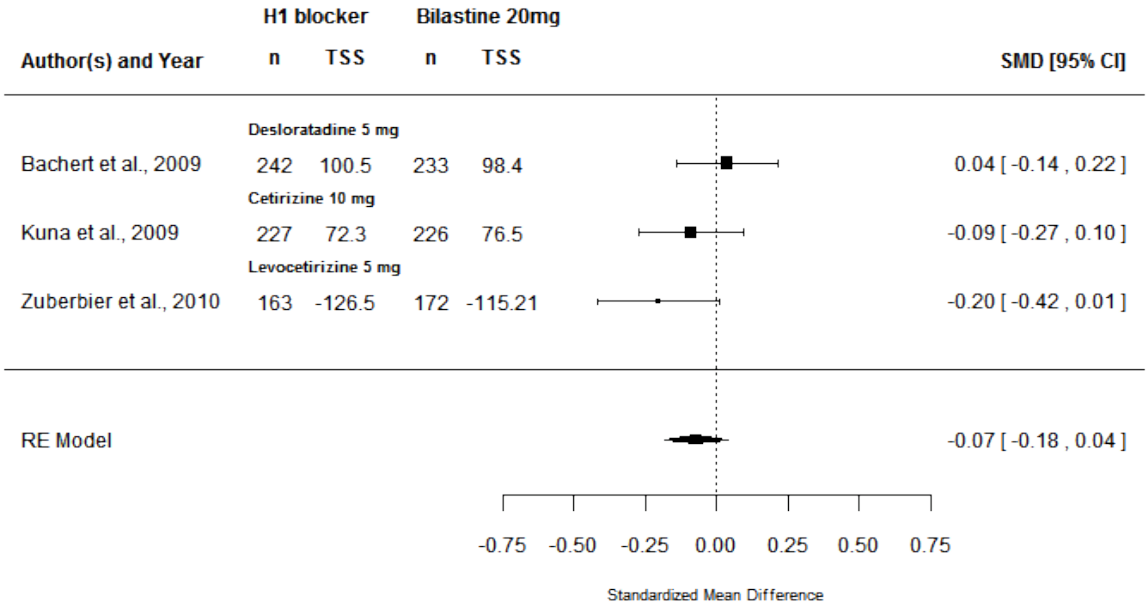

Figure 3. Forest plot showing the results of 3 studies examining the effectiveness of bilastine. The figure shows the standardized mean difference of total symptom scores (TSS) in the bilastine treated versus other H_1 blockers group with corresponding 95% confidence intervals in the individual studies and based on a random-effects model (p =.20). The H_1blocker and dose used in the study is shown above each corresponding study line.

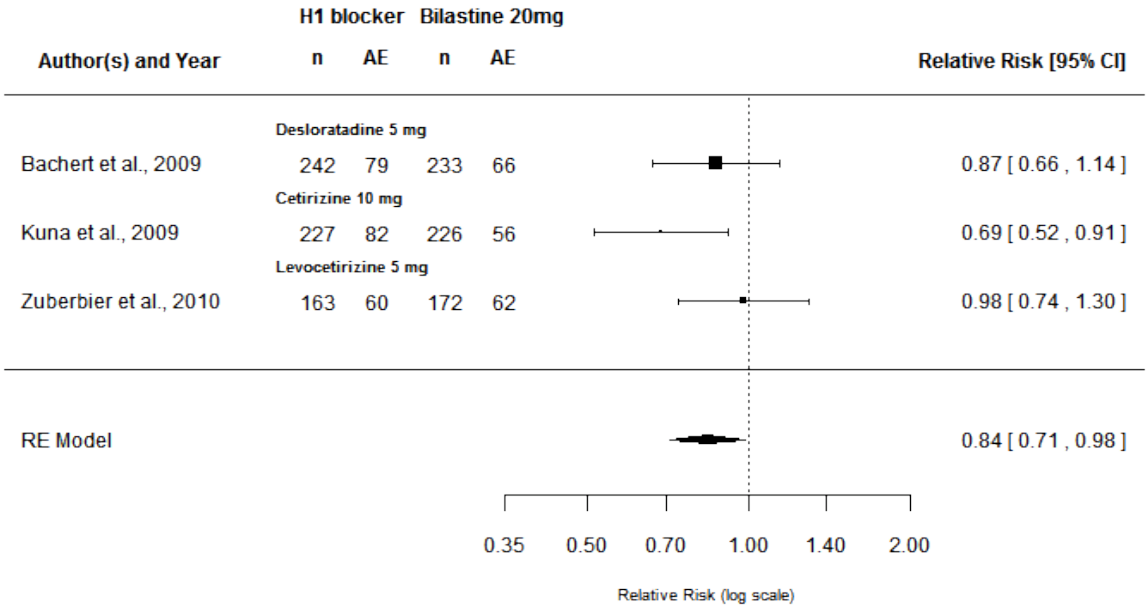

Figure 4. Forest plot showing the results of 3 studies examining the effectiveness of bilastine. The figure shows the relative risk of adverse events (AE) in the bilastine treated versus other H_1blockers group with corresponding 95% confidence intervals in the individual studies and based on a random-effects model (p =.03). The H_1blocker and dose used in the study is shown above each corresponding study line.

Table 1. Characteristics of reviewed clinical trials involving bilastine. Abbreviations: SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; CU, chronic idiopathic urticaria; AUC, area under the curve; TSS, total symptom score; TNSS, total nasal symptom score.

Source	Design and population	Primary outcome	Treatment regimens	Control regiment	Treatment duration	Jadad score (0 – 5)
Studies included in meta-analysis						
Bachert et al., 2009	Randomized, double-blind, placebo-controlled, parallel-group, multicenter; SAR	TSS AUC	Bilastine 20mg (n = 233); desloratadine 5mg (n = 242)	Placebo (n = 245)	14 days	4
Kuna et al., 2009	Randomized, double-blind, placebo-controlled, parallel-group, multicenter; SAR	TSS AUC	Bilastine 20mg (n = 226); cetirizine 10mg (n = 227)	Placebo (n = 225)	14 days	4
Zuberbier et al., 2010	Randomized, double-blind, placebo-controlled, parallel-group, multicenter; CU	TSS AUC change	Bilastine 20mg (n = 172); levocetirizine 5 mg (n = 163)	Placebo (n = 181)	28 days	4
Studies excluded from meta-analysis						
García-Gea et al., 2008	Crossover, randomized, double-blind, placebo-controlled, healthy volunteers	Wheal reaction after histamine challenge	Bilastine 20mg (n = 20); bilastine 40mg (n = 20); bilastine 80mg (n = 20); hydroxyzine 25mg (n = 20)	Placebo (n = 20)	7 days	3
Horak et al., 2010	Crossover, randomized, double-blind, placebo-controlled, SAR	TNSS after grass pollen challenge	Bilastine 20 mg (n = 74); cetirizine 10 mg (n = 68); fexofenadine 120 mg (n = 70)	Placebo (n = 70)	2 days	3
Sastre et al., 2012	Randomized, double-blind, placebo-controlled, parallel-group, multicenter; PAR	TSS AUC	Bilastine 20mg (n = 212); cetirizine 10mg (n = 214)	Placebo (n = 215)	28 days	4

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