

# Placebo-controlled assessment of somnolence effect of cetirizine: a meta-analysis

Qiong Du, MS and Yingchun Zhou, PhD

**Background:** It has been found that the most common adverse reaction which occurs more frequently on cetirizine than on placebo is somnolence. However, the somnolence rate varied widely among different studies. The objective of this study was to assess the somnolence effect of cetirizine 10 mg daily compared to placebo in patients aged 6 years and older using meta-analysis and explore the sources of heterogeneity among different studies.

**Methods:** Databases were searched for randomized controlled trials (RCTs) of cetirizine published before 2015. Overall risk differences (RDs) were determined by meta-analyses of 13 trials using the DerSimonian and Laird (D&L) method based on fixed-effects and random-effect models, respectively. The Q statistic, H statistic, and  $I^2$  were calculated for heterogeneity analysis. Subgroup analysis, Galbraith plot, sensitivity analysis, and meta-regression were also performed to explore the sources of heterogeneity.

**Results:** Various analyses showed that heterogeneity existed among the 13 trials and the placebo run-in period was the cause of heterogeneity. For RCTs without and with placebo run-in period, the overall RDs were 6.51% (95% CI,

4.47% to 8.56%) and 1.03% (95% CI, -0.13% to 2.19%), respectively, which indicated that the difference in somnolence rate between cetirizine 10 mg daily and placebo was not statistically significant for the subgroup with placebo run-in.

**Conclusion:** The meta-analysis showed that the RDs between cetirizine 10 mg daily and placebo on somnolence rate were different for studies with and without a placebo run-in period. The results for studies with a placebo run-in period suggested that cetirizine 10 mg daily has no somnolence effect compared to placebo. © 2016 ARS-AAOA, LLC.

## Key Words:

meta-analysis; cetirizine; somnolence; randomized controlled trial; heterogeneity; meta-regression; risk difference; placebo; sensitivity analysis

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Cetirizine is a well-known second-generation antihistamine drug that is safe and effective. Its indications are seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU). The systematic adverse effects of oral cetirizine are scarce, mainly including somnolence, dry mouth, and fatigue.<sup>1</sup> According

to the results from clinical trials performed in the United States and Canada targeted at subjects aged 12 years and older (sample size over 6000) with durations from 1 week to 6 months, the most common adverse reaction that occurred more frequently on cetirizine than on placebo was somnolence. The incidence of somnolence with cetirizine has been found to be dose-related, occurring in 6% of patients receiving placebo, and 14% of patients receiving 10 mg cetirizine.<sup>2</sup> However, somnolence rates reported for patients treated with cetirizine vary widely in published articles. In addition, some long-term observational studies indicated that the incidence of somnolence in cetirizine-treated patients is decreasing with continued use of the drug.<sup>3</sup>

We conducted a meta-analysis to assess the somnolence effect of cetirizine 10 mg daily compared to placebo in patients aged 6 years and older and to explore the sources of heterogeneity among different studies.

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TABLE 1. Summary of studies included in the meta-analysis

| First author | Publication year | Study location | Indication       | Usage    | Duration (weeks) | Placebo run-in period | Rescue medication | Inclusion criteria on age (years) | Subjects average age (years) | Male (%) | White (%) | Completion rate | Total Jadad score |
|--------------|------------------|----------------|------------------|----------|------------------|-----------------------|-------------------|-----------------------------------|------------------------------|----------|-----------|-----------------|-------------------|
| Falliers CJ  | 1991             | USA            | SAR              | 10 mg qd | 1 weeks          | No                    | No                | ≥ 18                              | 38.1                         | 68.20    | –         | –               | 4                 |
| Mansmann HC  | 1992             | USA            | PAR              | 10 mg qd | 4 weeks          | No                    | Yes               | ≥ 18                              | 34.6                         | 67.10    | –         | –               | 4                 |
| Masi M       | 1993             | Italy          | SAR              | 5 mg bid | 2 weeks          | No                    | No                | 6–12                              | 10.1                         | 61.3     | –         | 91.9            | 5                 |
| Breneman D   | 1995             | USA            | CIU              | 10 mg qd | 4 weeks          | No                    | No                | ≥ 12                              | 37.7                         | 27.0     | 80.0      | 75.5            | 3                 |
| Grant JA     | 1995             | USA            | SAR              | 10 mg qd | 6 weeks          | No                    | Yes               | 12–70                             | 28.4                         | 41.0     | 78.5      | 82.3            | 4                 |
| Meltzer EO   | 1996             | USA            | SAR              | 10 mg qd | 2 days           | No                    | No                | ≥ 12                              | 28.8                         | 50.0     | 86.0      | 97.8            | 4                 |
| Lockey RF    | 1996             | USA            | SAR              | 10 mg qd | 2 weeks          | No                    | Yes               | 12–70                             | 33.7                         | 40.2     | 81.7      | 91.0            | 4                 |
| Murray JJ    | 2002             | USA            | SAR              | 10 mg qd | 2 weeks          | Yes                   | No                | 18–65                             | 37.2                         | 34.0     | 82.6      | 93.9            | 4                 |
| Noonan MJ    | 2003             | USA            | SAR              | 10 mg qd | 2 weeks          | Yes                   | No                | 18–65                             | 36.6                         | 33.7     | 80.0      | 94.0            | 3                 |
| Fantin S     | 2008             | Europe         | PER <sup>a</sup> | 10 mg qd | 12 weeks         | No                    | No                | ≥ 12                              | 28.3                         | 34.7     | 99.3      | 88.2            | 4                 |
| Kuna P       | 2009             | Europe         | SAR              | 10 mg qd | 2 weeks          | No                    | No                | 12–70                             | 31.1                         | 47.6     | 99.4      | 94.9            | 5                 |
| Marmouz F    | 2011             | France         | PAR              | 10 mg qd | 4 weeks          | No                    | No                | ≥ 18                              | 32.1                         | 36.8     | 98.5      | –               | 3                 |
| Skoner DP    | 2014             | USA            | PAR              | 10 mg qd | 5 weeks          | Yes                   | No                | ≥ 18                              | 37.3                         | 29.7     | 84.7      | 92.8            | 4                 |

<sup>a</sup>The study indication in article Fantin S is PER; it was classified to the PAR category in the analyses. According to traditional classification criteria, rhinitis can be divided into SAR and PAR. In the ARIA classification, SAR and PAR were substituted by intermittent allergic rhinitis and PER, where SAR was equivalent to intermittent allergic rhinitis, and PAR was equivalent to the PER. ARIA = Allergic Rhinitis and its Impact on Asthma; bid = twice per day; CIU = chronic idiopathic urticaria; PAR = perennial allergic rhinitis; PER = persistent allergic rhinitis; qd = every day; SAR = seasonal allergic rhinitis.

**TABLE 2.** Treatment difference on somnolence rate

| Author                | Cetirizine 10 mg daily |    |      | Placebo |    |      | RD (%) | SE   | 95% CI            |
|-----------------------|------------------------|----|------|---------|----|------|--------|------|-------------------|
|                       | N                      | n  | %    | N       | n  | %    |        |      |                   |
| Falliers CJ           | 106                    | 24 | 22.6 | 103     | 6  | 5.8  | 16.82  | 4.67 | (7.65 to 25.98)   |
| Mansmann HC           | 72                     | 11 | 15.3 | 73      | 12 | 16.4 | -1.16  | 6.07 | (-13.05 to 10.73) |
| Masi M                | 63                     | 6  | 9.5  | 61      | 2  | 3.3  | 6.25   | 4.34 | (-2.27 to 14.76)  |
| Breneman D            | 62                     | 9  | 14.5 | 60      | 2  | 3.3  | 11.18  | 5.04 | (1.31 to 21.06)   |
| Grant JA              | 93                     | 8  | 8.6  | 93      | 3  | 3.2  | 5.38   | 3.44 | (-1.36 to 12.11)  |
| Meltzer EO            | 93                     | 12 | 12.9 | 93      | 2  | 2.2  | 10.75  | 3.79 | (3.33 to 18.18)   |
| Lockey RF             | 103                    | 12 | 11.7 | 105     | 3  | 2.9  | 8.79   | 3.55 | (1.83 to 15.76)   |
| Murray JJ             | 431                    | 9  | 2.1  | 431     | 4  | 0.9  | 1.16   | 0.83 | (-0.47 to 2.79)   |
| Noonan MJ             | 202                    | 3  | 1.5  | 198     | 1  | 0.5  | 0.98   | 0.99 | (-0.96 to 2.92)   |
| Fantin S              | 175                    | 14 | 8    | 185     | 8  | 4.3  | 3.68   | 2.54 | (-1.30 to 8.65)   |
| Kuna P                | 228                    | 17 | 7.5  | 226     | 5  | 2.2  | 5.24   | 2.00 | (1.33 to 9.16)    |
| Marmouz F             | 66                     | 4  | 6.1  | 70      | 0  | 0    | 6.06   | 2.94 | (0.30 to 11.82)   |
| Skoner DP             | 158                    | 4  | 2.5  | 162     | 3  | 1.9  | 0.68   | 1.64 | (-2.53 to 3.89)   |
| Overall random effect |                        |    |      |         |    |      | 4.45   | 1.07 | (2.35 to 6.55)    |
| Overall fixed effect  |                        |    |      |         |    |      | 2.37   | 0.52 | (1.36 to 3.38)    |

CI = confidence interval; N = number of treated subjects; n = number of subjects reporting somnolence; RD = risk difference; SE = standard error.

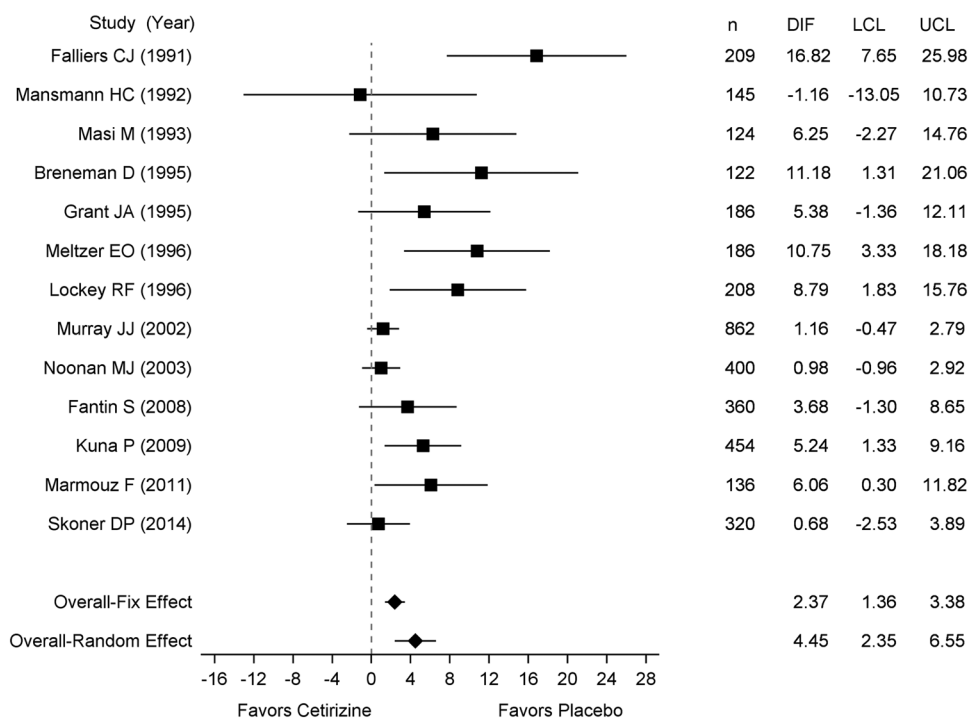


**FIGURE 1.** Risk differences between cetirizine 10 mg daily and placebo on somnolence as well as their 95% CIs. CI = confidence interval; DIF = risk difference; LCL = lower confidence limit; UCL = upper confidence limit.

**TABLE 3.** Subgroup analysis of cetirizine effect on somnolence compared to placebo

| Subgroup variable                | Model         | Risk difference (%) | Standard error | 95% CI           |
|----------------------------------|---------------|---------------------|----------------|------------------|
| <b>Study location</b>            |               |                     |                |                  |
| North America                    | Fixed-effect  | 1.88                | 0.56           | (0.79 to 2.98)   |
|                                  | Random-effect | 4.35                | 1.37           | (1.66 to 7.04)   |
| Europe                           | Fixed-effect  | 5.08                | 1.32           | (2.49 to 7.66)   |
|                                  | Random-effect | 5.08                | 1.32           | (2.49 to 7.66)   |
| <b>Publication year</b>          |               |                     |                |                  |
| Before 2000                      | Fixed-effect  | 8.55                | 1.58           | (5.45 to 11.65)  |
|                                  | Random-effect | 8.56                | 1.78           | (5.07 to 12.06)  |
| After 2000                       | Fixed-effect  | 1.64                | 0.54           | (0.57 to 2.71)   |
|                                  | Random-effect | 1.95                | 0.74           | (0.50 to 3.40)   |
| <b>Study duration</b>            |               |                     |                |                  |
| <1 Week                          | Fixed-effect  | 10.75               | 3.79           | (3.33 to 18.18)  |
|                                  | Random-effect | 10.75               | 3.79           | (3.33 to 18.18)  |
| ≥ 1 Week                         | Fixed-effect  | 2.21                | 0.52           | (1.19 to 3.23)   |
|                                  | Random-effect | 3.95                | 1.04           | (1.92 to 5.99)   |
| <b>Indication</b>                |               |                     |                |                  |
| SAR                              | Fixed-effect  | 2.29                | 0.57           | (1.17 to 3.41)   |
|                                  | Random-effect | 5.20                | 1.45           | (2.37 to 8.04)   |
| Other                            | Fixed-effect  | 2.72                | 1.19           | (0.40 to 5.05)   |
|                                  | Random-effect | 3.42                | 1.68           | (0.13 to 6.72)   |
| <b>Inclusion criteria on age</b> |               |                     |                |                  |
| 6–12 years                       | Fixed-effect  | 6.25                | 4.34           | (–2.27 to 14.76) |
|                                  | Random-effect | 6.25                | 4.34           | (–2.27 to 14.76) |
| ≥ 12 years                       | Fixed-effect  | 2.32                | 0.52           | (1.30 to 3.33)   |
|                                  | Random-effect | 4.39                | 1.11           | (2.22 to 6.56)   |
| <b>Placebo run-in period</b>     |               |                     |                |                  |
| No                               | Fixed-effect  | 6.51                | 1.04           | (4.47 to 8.56)   |
|                                  | Random-effect | 6.71                | 1.18           | (4.40 to 9.03)   |
| Yes                              | Fixed-effect  | 1.03                | 0.59           | (–0.13 to 2.19)  |
|                                  | Random-effect | 1.03                | 0.59           | (–0.13 to 2.19)  |
| <b>Rescue medication</b>         |               |                     |                |                  |
| No                               | Fixed-effect  | 2.19                | 0.53           | (1.15 to 3.22)   |
|                                  | Random-effect | 4.26                | 1.16           | (1.99 to 6.54)   |
| Yes                              | Fixed-effect  | 5.86                | 2.29           | (1.38 to 10.35)  |
|                                  | Random-effect | 5.84                | 2.32           | (1.30 to 10.39)  |

CI = confidence interval; SAR = seasonal allergic rhinitis.

**TABLE 4.** Analyses of heterogeneity by subgroup variables

| Subgroup variables | Category  | Q statistic | p     | H statistic | 95% CI of H   | I <sup>2</sup> | 95% CI of I <sup>2</sup> |
|--------------------|-----------|-------------|-------|-------------|---------------|----------------|--------------------------|
| Study location     | Europe    | 0.496       | 0.920 | 0.407       | (0.159–1.039) | 0.000          | (0.000–0.074)            |
|                    | America   | 26.293      | 0.001 | 1.813       | (1.284–2.560) | 0.696          | (0.393–0.847)            |
| Publication year   | <2000     | 7.440       | 0.282 | 1.114       | (0.754–1.644) | 0.194          | (0.000–0.630)            |
|                    | ≥2000     | 7.292       | 0.200 | 1.208       | (0.769–1.897) | 0.314          | (0.000–0.722)            |
| Study duration     | ≥1 Week   | 26.770      | 0.005 | 1.560       | (1.134–2.146) | 0.589          | (0.223–0.783)            |
| Indication         | SAR       | 25.432      | 0.001 | 1.906       | (1.332–2.728) | 0.725          | (0.436–0.866)            |
|                    | Others    | 6.217       | 0.184 | 1.247       | (0.763–2.037) | 0.357          | (0.000–0.759)            |
| Patient age group  | ≥12 years | 30.952      | 0.001 | 1.677       | (1.232–2.284) | 0.645          | (0.341–0.808)            |
| Placebo run-in     | No        | 10.773      | 0.292 | 1.094       | (0.779–1.537) | 0.165          | (0.000–0.577)            |
|                    | Yes       | 0.073       | 0.964 | 0.191       | (0.062–0.592) | 0.000          | (0.000–0.000)            |
| Rescue medication  | No        | 27.267      | 0.001 | 1.741       | (1.248–2.429) | 0.670          | (0.357–0.830)            |
|                    | Yes       | 2.040       | 0.361 | 1.010       | (0.326–3.132) | 0.020          | (0.000–0.898)            |

CI = confidence interval; SAR = seasonal allergic rhinitis.

## Materials and methods

### Search strategy

We performed a systematic review of the medical literature for randomized, double-blinded, parallel placebo-controlled trials that reported the effect of cetirizine 10 mg daily on somnolence. We searched PubMed, PMC, ScienceDirect, Wiley, and CENTRAL (Cochrane Central Register of Controlled Trials) computerized bibliographic databases (1966 to 2015). We did not search for abstracts or attempted to identify unpublished data (eg, pharmaceutical companies, the U.S. Food and Drug Administration [FDA], etc.). The search was performed by combining the Medical Subject Heading (MESH) “cetirizine,” “somnolence,” “placebo,” and combinations of the words. The search was restricted to English.

### Study inclusion criteria

#### Study

Only double-blinded, randomized clinical trials (RCTs) were included in the analysis. Trials performed in the Environmental Exposure Unit (EEU) were not included. Only studies with full-text articles accessible were included. Unpublished articles were not included.

#### Population

To be consistent with the label of cetirizine, only studies with indications stated as SAR, PAR, and CIU were included in the study. In addition, the target population was limited to patients aged 6 years or older.

#### Intervention

Both cetirizine 10 mg daily and placebo groups were required for a study to be included; studies that only had 1 of the 2 treatment groups were not included.

**TABLE 5.** Meta-regression analyses on subgroup variables

| Subgroup variables       | F statistic | p     |
|--------------------------|-------------|-------|
| Study location           | 0.001       | 0.970 |
| Article publication year | 6.238       | 0.030 |
| Study duration           | 2.370       | 0.152 |
| Study indication         | 1.772       | 0.210 |
| Patient age group        | 0.114       | 0.743 |
| Placebo run-in period    | 20.912      | 0.001 |
| Rescue medication        | 0.696       | 0.422 |

### Outcome

Studies were included if they provided the following information: the total numbers of subjects in the cetirizine 10 mg daily and placebo groups as well as the number or percentage of subjects reporting somnolence in the 2 groups.

### Data abstraction and validity assessment

The full texts of all selected articles were reviewed independently by the authors to confirm study eligibility and assess study quality. Disagreement between reviewers was resolved by consensus. Data were extracted using a pre-designed extraction form. Trials fulfilling the inclusion criteria were scored for quality using the criteria established by the Jadad scale.<sup>4</sup>

The extracted data included: first author of articles, publication year, study location, study indication, medication usage, study duration, whether rescue medications were allowed, inclusion criteria on age, mean age of subjects, gender and race of subjects, completion rate,

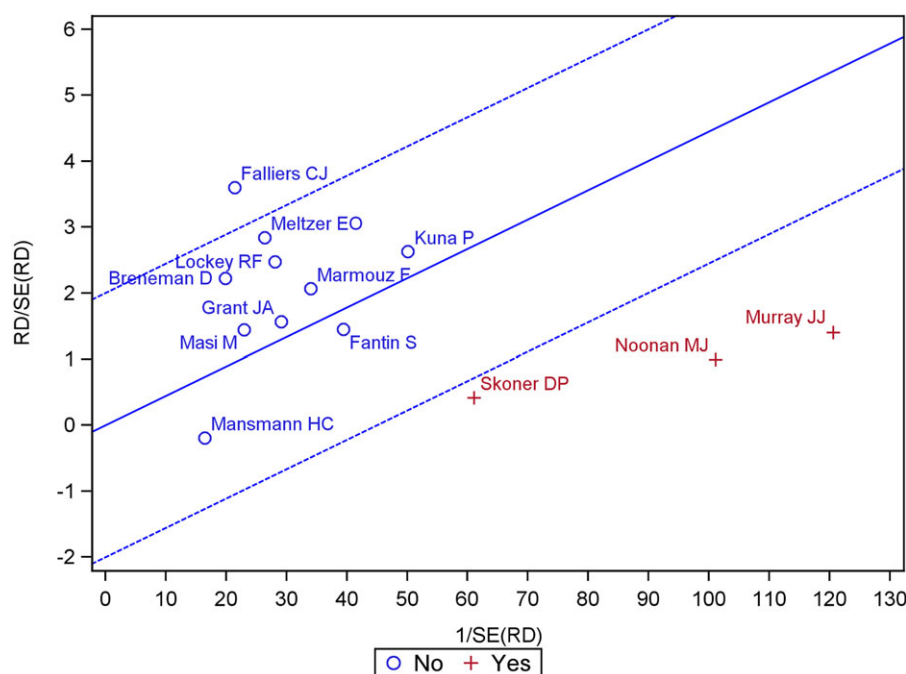


**FIGURE 2.** Galbraith plot by placebo run-in period. RD = risk difference; SE = standard error.

number of the randomized subjects, and number or percent of subjects reporting somnolence in each treatment group.

### Data analysis

All statistical analyses were performed using version 9.4 of SAS software (SAS Institute, Cary, NC).

An overall risk difference (RD) in somnolence rate with 95% confidence intervals (CIs) was calculated using the DerSimonian and Laird (D&L)<sup>5</sup> method based on fixed-effect and random-effect models, respectively.

Heterogeneity among studies was calculated using Q statistic.<sup>6</sup> Significant heterogeneity was defined by a *p* value of 0.10 or less. H statistic<sup>7</sup> and I<sup>2</sup> statistics<sup>7,8</sup> were also calculated. Besides the above tests and statistics, subgroup analysis, Galbraith graph,<sup>9,10</sup> sensitivity analysis and meta-regression<sup>11,12</sup> were performed to explore the possible sources of heterogeneity.

Subgroup analyses were separately performed for publication year, study location, cetirizine usage, study indication, duration, with or without placebo run-in period, inclusion criteria on age, and whether rescue medications were allowed.

The sensitivity analyses were performed using the leave-1-out method, which removes 1 study at a time and calculates the combined effect size of the rest of studies using DerSimonian and Laird method to understand the effect of each removed study on the combined effect size.

Possible potential publication bias was discussed. The trim and fill method<sup>13–15</sup> was performed to obtain the adjusted results.

## Results

### Literature search

A total of 230 articles were identified according to the keywords; 28 articles<sup>2,16–42</sup> that described the number or proportion of somnolence occurred in cetirizine and placebo groups. Among these 28 articles, 13 articles<sup>16–28</sup> that met the inclusion/exclusion criteria and provided enough information were included in this meta-analysis; see Table 1 for their descriptions. In these 13 studies, subjects were comparable between treatments in age, gender, and other demographic variables; the rates of noncompliance and loss to follow-up were controlled at a reasonable low level.

### Quality assessment

Ten of the studies eligible for this meta-analysis had a Jadad score of 4 or 5 (see Table 1), and 3 studies had a score of 3, demonstrating good quality of the study designs.

### Overall RD

Table 2 and Figure 1 present the overall RDs between cetirizine 10 mg daily and placebo on somnolence based on fixed-effect and random-effect models, respectively, as well as the RD and its 95% CI for each study. Observe that the RDs for individual studies ranged from –1.16% to 16.82%. Among the 13 studies, 7 of them have 95% CIs of RD containing zero, which indicates that the difference in somnolence between cetirizine 10 mg daily and placebo was not statistically significant. For the other 6 studies, the difference was statistically significant. The overall RD for the fixed-effect model was 2.37% (95% CI, 1.36% to

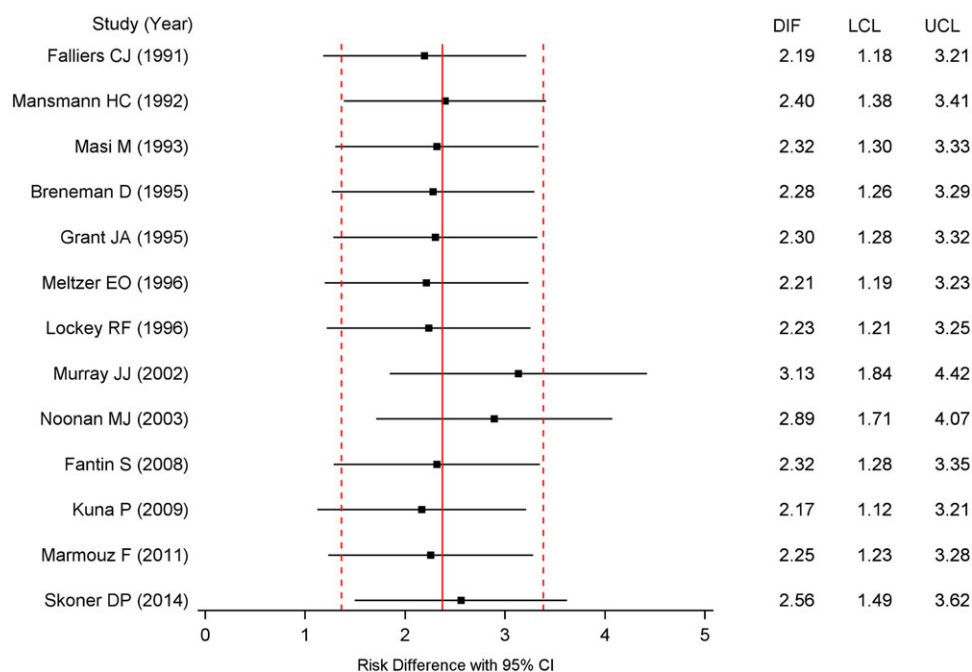


**FIGURE 3.** Sensitivity analysis (leave-1-out) of risk differences between cetirizine 10 mg daily and placebo on somnolence as well as their 95% CIs based on the fixed-effect model. CI = confidence interval; DIF = risk difference; LCL = lower confidence limit; UCL = upper confidence limit.

3.38%), and that for the random-effect model was 4.45% (95% CI, 2.35% to 6.55%). The 2 were a little different; later heterogeneity tests were performed to formally test whether there was heterogeneity among the 13 studies.

### Heterogeneity test

The test for heterogeneity was significant ( $Q = 31.758$ ,  $p = 0.002$ ).  $H$  value was greater than 1.5 ( $H = 1.627$ ; 95% CI, 1.205 to 2.197) and  $I^2$  was greater than 0.5 ( $I^2 = 0.622$ ; 95% CI, 0.311 to 0.793), all of them suggested that there was heterogeneity among the 13 studies.

### Subgroup analyses

Subgroup analyses were performed on 8 possible heterogeneity factors, respectively: publication year (before 2000, after 2000), study location (Europe, North America), cetirizine usage, study indication (SAR, other), study duration (<1 week,  $\geq 1$  week), whether there was placebo run-in period (yes, no), inclusion criteria on age (6 to 12 years,  $\geq 12$  years), whether rescue medications were allowed (yes, no). Because the classifications by cetirizine usage and inclusion criteria on age were completely the same, only 1 of these 2 factors was included in the following analyses.

It can be seen from Table 3 that there was big difference between the results from the random-effect and fixed-effect model in the studies located in North America, with duration at least 1 week, indication being SAR, inclusion criteria on age at least 12 years, and rescue medication being allowed, which indicated that the studies with these features were heterogeneous. The results of the subgroup heterogeneity analyses (Table 4) confirmed the heterogeneity in

these groups. These suggested that these factors are not the causes of heterogeneity because one could not eliminate the heterogeneity among studies by dividing the studies using these factors. On the contrary, little difference was found between the results from the random-effect and fixed-effect models for studies classified by publication year and with/without placebo run-in period, which suggested that these 2 factors may be the sources of heterogeneity.

### Meta-regression

Table 5 lists the  $p$  values for each of the subgroup variables based on the random-effect meta-regression analyses. It can be seen that at the significance level of 0.05, the study location, study duration, study indication, inclusion criteria on age, and whether rescue medications were allowed were not statistically significant, so they were not considered as the cause of the heterogeneity; however, the publication year and with/without placebo run-in period were statistically significant ( $p = 0.030$  and  $0.001$ , respectively).

Another meta-regression analysis was performed that included both publication year and with/without placebo run-in period in the random-effect model. After adjusting the effect of each other, the factor with/without placebo run-in period was still statistically significant ( $p = 0.026$ ), but the publication year was not statistically significant ( $p = 0.118$ ). Hence, the factor with/without placebo run-in period was considered the only true source of heterogeneity.

### Galbraith plots

As can be seen from Figure 2, the 3 studies with placebo run-in period—Falliers CJ, Meltzer EO, and Skoner

DP—form a cluster that is clearly separated from the cluster of the other 10 studies without placebo run-in period.

### Sensitivity analyses

The results of the sensitivity analyses for the fixed-effect model are shown in Figure 3. It can be seen that the 3 studies with placebo run-in period had the largest influence on the variation of the overall RD, which once more indicated that with/without placebo run-in period is a source of heterogeneity.

### Publication bias

Publication bias may exist because whether research findings were published may depend on whether they were statistically significant. However, because the primary objective of the studies included in the meta-analysis mainly focused on the efficacy of cetirizine, not safety, and no statistical inferences were performed for somnolence rate, whether the results were published did not depend on the somnolence rate. Moreover, in the label of cetirizine, somnolence was stated as the most common adverse event and the somnolence rate (14% for 10 mg daily) was also stated; it was not necessary not to publish the study results due to the somnolence rate.

In case publication bias exists, using the trim and fill method, we estimated the overall effect size for the fixed-effect model to be 1.49 (95% CI, 0.53 to 2.45), and for the random-effect model to be 1.73 (95% CI, -0.55 to 4.01).

### Discussion

According to the results of the meta-analysis, the overall RDs of the 13 studies based on the fixed-effect and random-effect model were 2.37% (95% CI, 1.36% to 3.38%) and 4.45% (95% CI, 2.35% to 6.55%), respectively. Both of the 2 estimates were lower than the 8% that is stated in the label of cetirizine, and both of the 95% CIs did not contain zero, which indicated that the difference on somnolence between cetirizine 10 mg daily and placebo was statistically significant. However, the results of heterogeneity tests Q test, H value, and  $I^2$  all showed that there was heterogeneity among the 13 studies, undermining the assumption of the fixed-effect model, so the RD estimate based on the fixed-effect model was not credible.

The results of various analyses to explore heterogeneity found that with/without placebo run-in period was the only source of heterogeneity. Moreover, placebo run-in period as the cause of heterogeneity was clinically meaningful. Many recent studies showed that<sup>43–45</sup> allergic rhinitis itself was 1 of the causes of daytime somnolence due to congestion and blocked nasal passage caused by chronic

inflammation of nasal mucosa. As the indication itself could cause somnolence, its effect should be eliminated or controlled when the treatment effect on somnolence was studied, which was the reason that placebo run-in period was introduced into the study design. In the guidance for industry by the FDA in 2000 “Allergic Rhinitis: Clinical Development Programs for Drug Products,” it stated that “These studies should be double-blinded, placebo-controlled, and parallel group, preferably with a placebo run-in period.”

In the subgroup meta-analysis, the overall RD for the 10 studies without placebo run-in period based on the fixed-effect model was 6.51%, close to the 8% stated in the label for cetirizine. The 95% CI (4.47% to 8.56%) did not include zero, indicating that the difference on somnolence rate between cetirizine 10 mg daily and placebo was statistically significant for this group. For the studies with placebo run-in period, the overall RD based on the fixed effect model was 1.03%, which was far lower than 8%. The 95% CI (-0.13% to 2.19%) included zero, indicating that the difference on somnolence rate was not statistically significant for this group. Although there were only 3 studies with placebo run-in period, their sample sizes are the largest (Murray JJ), the third largest (Noonan MJ), and the fifth largest (Skoner DP) among all studies, and the sum of the sample sizes of the 3 studies accounted for around 43% of the total sample sizes of the 13 studies. The large sample sizes resulted in a 95% CI with reasonable length (-0.13% to 2.19%); therefore, the result is meaningful.

As mentioned above, the somnolence rate for studies without placebo run-in period was the combined effect of treatment and disease because the effect of allergic rhinitis on daytime somnolence was not controlled in such studies, while the results for those with placebo run-in period was mainly from treatment itself. Therefore the RD for the studies with placebo run-in period can disclose the real effect of cetirizine on somnolence compared to placebo. This suggested that cetirizine 10 mg daily has no statistically significant somnolence effect compared to placebo.

### Conclusion

The meta-analysis showed that the RDs between cetirizine 10 mg daily and placebo on somnolence rate were different for studies with and without a placebo run-in period. The results for studies with a placebo run-in period suggested that cetirizine 10 mg daily has no somnolence effect compared to placebo. ④

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