

Comparison of the sedating effects of levocetirizine and cetirizine: a randomized, double-blind, placebo-controlled trial

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Background: Compared with placebo, levocetirizine has been found to be less sedating than cetirizine in separate trials. However, whether levocetirizine is less sedating than its parent drug cetirizine has not yet been studied in a randomized trial.

Objective: To determine whether levocetirizine is less sedating than cetirizine.

Methods: We conducted a randomized, double-blind, crossover, placebo-controlled trial examining sedation and allergy symptoms in patients with perennial allergic rhinitis who had previously reported significant sedation with cetirizine. Enrollment ran from January 28, 2009, to February 25, 2009. All patients completed the study by April 17, 2009. Thirty patients enrolled, and 29 patients completed the study (1 patient did not return her questionnaire). In a double-blind fashion, the 29 study participants received levocetirizine, 5 mg daily for 1 week, cetirizine, 10 mg daily for 1 week, and an equivalent placebo pill for 1 week in randomized order with washout periods before each treatment arm. At the end of each washout period and each treatment period, participants completed a 1-page questionnaire. This questionnaire included questions about sedation or sleepiness in the form of a modified Epworth Sleepiness Scale, a Likert scale measuring general or global sedation, and allergy symptoms as measured by the total rhinitis symptom score.

Results: Sedation as measured by both the modified Epworth Sleepiness Scale and the Likert scale was not significantly different between the levocetirizine and cetirizine treatments.

Conclusions: In patients with a perceived history of sedation with cetirizine, most were able to tolerate levocetirizine. However, this controlled trial also suggests that many of these patients would tolerate cetirizine if given in a masked manner. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine.

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INTRODUCTION

Cetirizine is one of the most potent second-generation antihistamines as measured by surrogate markers of effectiveness, such as suppression of skin reactivity to histamine (wheal-and-flare inhibition).¹ The newest antihistamine available, levocetirizine, is the R-enantiomer of cetirizine. Studies on histamine suppression found that 2.5 mg of levocetirizine is comparable to 5 mg of cetirizine, suggesting that the antihistamine properties of cetirizine may be attributable to its levocetirizine enantiomer alone.² Surprisingly, some data suggest that levocetirizine has 2-fold increased affinity for histamine₁-receptors over that of cetirizine

alone.³ Levocetirizine possesses higher receptor occupancy at 24 hours than either desloratadine or fexofenadine.⁴ In most studies comparing the effects of levocetirizine to desloratadine, levocetirizine had a faster onset of action and greater consistency of effect than desloratadine.⁵ Similarly, one study found levocetirizine to produce greater wheal-and-flare inhibition than other well-established second-generation antihistamines, such as fexofenadine and loratadine.⁶

As with the other second-generation antihistamines, levocetirizine was found to be superior to placebo in the relief of symptoms of allergic rhinitis and quality-of-life measures.^{7,8} One randomized, double-blind, placebo-controlled trial of cetirizine vs levocetirizine use in children examined quality-of-life measures and symptom scores and concluded that cetirizine was more effective than levocetirizine.⁹ In contrast, in an open-label, observational study of 7,274 European patients treated with various antihistamines, levocetirizine scored significantly higher than other antihistamines in terms of perception of efficacy, tolerability, and overall satisfaction for both physician and patient ratings.¹⁰ In this same study, the rate of somnolence in the levocetirizine group (3.8%) was similar to that for fexofenadine and desloratadine and less than half the rate for cetirizine.

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Compared with placebo, levocetirizine has been found to be less sedating than cetirizine in separate trials (6% for levocetirizine vs 2% for placebo¹¹ and 14% cetirizine vs 6% for placebo¹²). However, whether levocetirizine is less sedating than its parent drug cetirizine has not yet been studied in a head-to-head, double-blind, placebo-controlled, randomized trial.

Initially, we performed a pilot study examining patient-reported sedation with cetirizine and levocetirizine. A retrospective medical record review was completed for 469 patients seen at the university allergy clinic who were prescribed levocetirizine between January 1, 2008, and June 30, 2008. Using *levocetirizine* as a search term in the electronic medical record, all patients who had been prescribed levocetirizine were identified. Then, patients' clinic notes were reviewed to see whether they had been changed from cetirizine to levocetirizine due to sedation. Patients were contacted by telephone to confirm that they had been switched to levocetirizine due to their own perception that cetirizine was too sedating to continue due to interference with activities of daily living. Of the 45 patients who had been switched from cetirizine to levocetirizine due to sedation with cetirizine, 33 (73%) reported being able to tolerate levocetirizine. Therefore, in this medical record review, levocetirizine was subjectively less sedating than cetirizine most of the time.¹³

Given the results of the pilot study, we hypothesized that levocetirizine would be subjectively less sedating than cetirizine in a randomized, double-blind, placebo-controlled trial.

METHODS

Vanderbilt University institutional review board approval was obtained. We examined patients with perennial allergic rhinitis who had a history of significant sedation or somnolence when taking cetirizine. Twenty-eight of 29 patients had never taken levocetirizine. Each patient, in a crossover design, received levocetirizine, cetirizine, and placebo in randomized order.

Eligible patients who satisfied the inclusion and exclusion criteria were offered enrollment in the study, and written informed consent was obtained. Most patients were recruited through a medical center e-mail listserv and by posted flyers at the university allergy clinic. A few patients were recruited via personal recruitment or telephone solicitation of patients who were seen regularly at the Vanderbilt University allergy clinic. Enrollment ran from January 28, 2009, to February 25, 2009. All patients completed the study by April 17, 2009. Thirty patients enrolled, and 29 patients completed the study (1 patient did not return her questionnaire). Interested patients who had not had allergy testing within the last 3 years underwent skin testing to inhalants to see whether they met the required criteria below.

Patients who were 18 to 77 years old and who had perennial allergic rhinitis to dust mite or cat or dog (the latter 2 only if relevant) with or without seasonal allergic rhinitis were recruited for the study. Mold and cockroach sensitiza-

tion was not considered because levels of exposure would have been too variable; also efficacy of antihistamine was not the primary end point. Patients must have reported moderate or severe sedation with cetirizine, and they must have tried cetirizine for at least a week before stopping its use. Moderate sedation was considered being only able to tolerate 5 mg of cetirizine or a 10-mg dose only at night because of patient-perceived interference with normal activities of daily living. Severe sedation was considered being unable to tolerate continued cetirizine use even at lower than normal doses or with nighttime use because of patient-perceived interference with normal activities of daily living. Exclusion criteria included any condition that required ongoing antihistamine or steroid treatment for which the patient was unable or unwilling to stop use of antihistamines during washout periods, recent sinusitis, nonallergic rhinitis, or the presence of a sleep disorder, such as sleep apnea.

Randomization of each patient in regard to the order of medications they received (cetirizine, levocetirizine, and placebo, each for 1 week) took place by computer program randomization. In a double-blind manner, study participants received levocetirizine, 5 mg daily for 1 week, cetirizine, 10 mg daily for 1 week, and an equivalent placebo pill for 1 week. An equivalent placebo capsule with no active ingredient was prepared by the Vanderbilt Investigational Drug Service pharmacy. The order of these 3 weeks was randomly assigned to each patient in the study. There was a 5-day washout period at the beginning of the study in which each patient was asked not to take any prescription or over-the-counter oral antihistamine.

At the end of the 5-day washout period, participants completed a baseline questionnaire that included questions about sedation or sleepiness in the Epworth Sleepiness Scale (ESS),¹⁴ a Likert scale constructed by the investigators that measured global sedation, and a total rhinitis symptom score (TRSS). We constructed the Likert scale, which was anchored as follows: 1, not at all sedated; 3, mildly sedated; 5, moderately sedated; 7, very sedated; and 9, extremely sedated. On the basis of this construction, we theorized that the minimally significant difference between scores would have to cross the anchored categories. Therefore, we chose a value of 2 to be the minimally significant clinical difference. Indeed, this study was sufficiently powered to detect a mean difference of 2 or greater in the Likert scores between the cetirizine arm and the levocetirizine arm. The TRSSs assessed allergy symptoms of "itchy nose, itchy eyes, runny nose, and sneezing" on a scale of 0 to 4 (0, absent; 1, mild; 2, moderate; and 3, severe). The TRSS has been used in previous studies validating the efficacy of antihistamines.¹⁵ Patients were sent reminder e-mails when it was time to fill out the next questionnaire and transition to the next phase of the study.

After each of the first 2 weeks there were additional 5-day washout periods in which patients were asked not to take any oral antihistamine before resuming the next study medication. Thus, a patient might be randomly assigned to the following,

for example: cetirizine, 10 mg daily for 1 week, then wait 5 days, then start levocetirizine, 5 mg daily for 1 week, then wait 5 days, then placebo daily for 1 week. At the beginning of the study (after the initial washout period), at the end of each subsequent washout period, and at the end of each intervention week (cetirizine, levocetirizine, or placebo), participants filled out sedation score cards and TRSS cards (standardized symptom cards rating allergy symptoms of nasal pruritus, ocular pruritus, rhinorrhea, and sneezing). These TRSSs were rated on a 0- to 3-point scale, where 0 indicates absent and 3 indicates severe. Questionnaires were completed on days 5, 12, 17, 24, 29, and 36, corresponding to the ends of each 7-day intervention period and each 5-day washout period. Patients who completed the study were compensated for their time and participation with a \$50 check.

Power Analysis

A 2-unit difference in the Likert scale scores of sedation outcome between the cetirizine and levocetirizine groups was thought by the investigators to correspond to the minimal clinically significant difference of interest. In particular, a difference of 2 units crosses anchors in the Likert scale (1, not at all sedated; 3, mildly sedated; 5, moderately sedated; 7, very sedated; and 9, extremely sedated). Similarly, a 2-point difference in repeated ESS scores had been described as the minimal clinically significant difference in previous studies.¹⁶ On the basis of this, a sample size of 30 patients was determined to be needed to detect a 2-unit (or greater) difference in mean ESS (or Likert scale score) between the cetirizine and levocetirizine groups with 80% power, using a paired

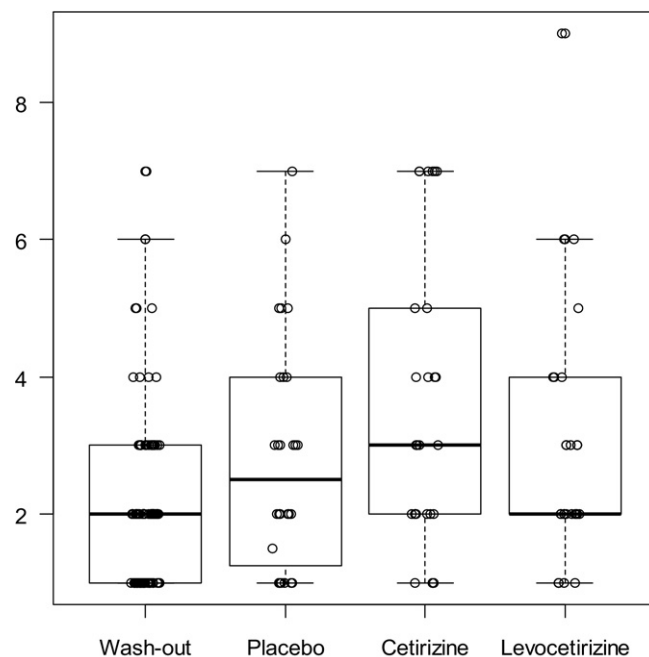


Figure 2. Likert scores (range, 1-9) across periods.

2-sample *t* test and assuming a (2-sided) type I error rate of 5% and an SD of 4 units. Note, because the calculation was based on a paired *t* test (because of the study's crossover design), the SD represents the standard deviation of the difference in the repeated outcomes for a given individual.

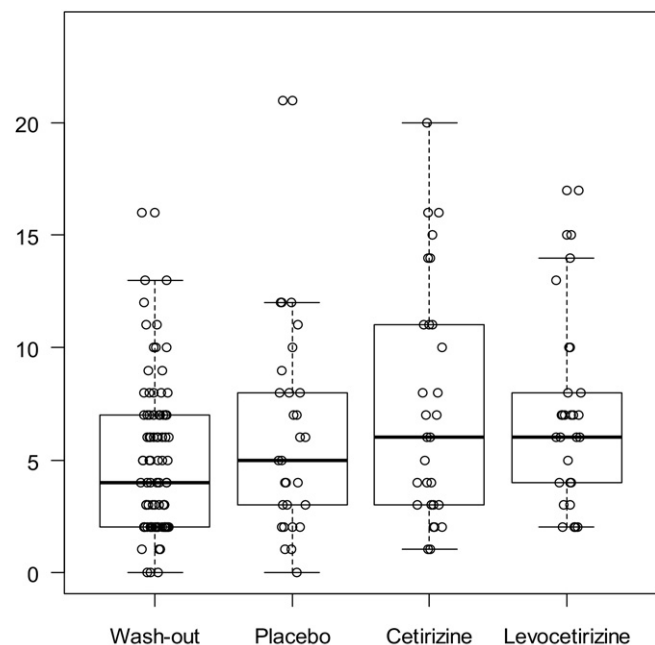


Figure 1. Modified Epworth Sleepiness Scale scores (range, 0-24) across periods.

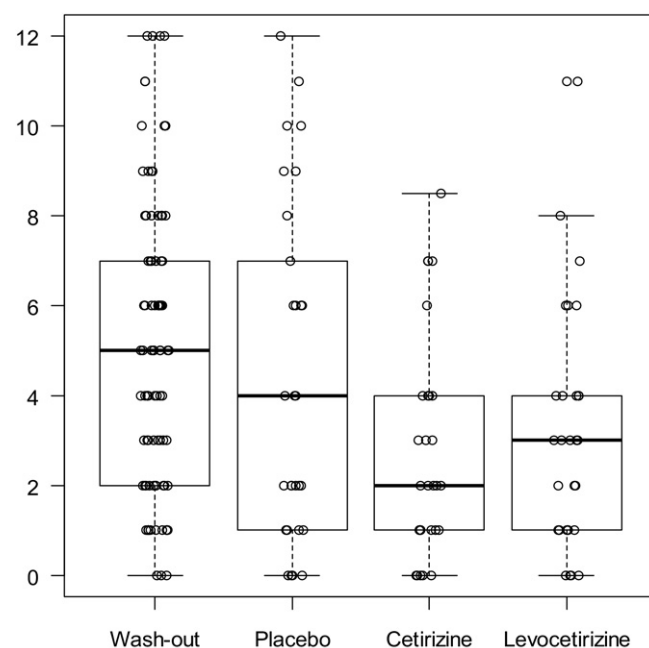


Figure 3. TRSS (range, 0-12) across periods.

Table 1. Comparison of Outcomes Across Drugs

Scale	No. of nonmissing values	Lower quartile/median/upper quartile (mean $\pm$ SD)			
		Placebo (n = 29)	Cetirizine (n = 29)	Levocetirizine (n = 29)	Combined (n = 87)
ESS	87	3.00/5.00/8.00 (6.14 $\pm$ 4.58)	3.00/6.00/11.00 (7.48 $\pm$ 5.31)	4.00/6.00/8.00 (6.69 $\pm$ 4.05)	3.00/6.00/9.50 (6.77 $\pm$ 4.65)
Likert	83	1.38/2.50/4.00 (2.80 $\pm$ 1.67)	2.00/3.00/5.00 (3.54 $\pm$ 2.17)	2.00/2.00/4.00 (3.07 $\pm$ 1.92)	2.00/3.00/4.00 (3.14 $\pm$ 1.93)
TFSS	87	1.00/4.00/7.00 (4.41 $\pm$ 3.76)	1.00/2.00/4.00 (2.67 $\pm$ 2.44)	1.00/3.00/4.00 (3.14 $\pm$ 2.67)	1.00/2.00/6.00 (3.41 $\pm$ 3.06)

Abbreviations: ESS, Epworth Sleepiness Scale; TRSS, total rhinitis symptom score.

Statistical Analysis

Nonparametric Wilcoxon signed-rank (ie, paired) tests were used (1) to determine whether the distribution of each outcome (ESS score, Likert scale scores, and TRSS) was significantly different between the cetirizine and levocetirizine medication periods, (2) to determine whether the distribution of each outcome was significantly different between the placebo and each of the 2 medication (cetirizine and levocetirizine) periods, and (3) to determine whether the distribution of each outcome was significantly different between each pair of washout periods (ie, 1 vs 3, 1 vs 5, and 3 vs 5). $P < .05$ was considered significant. No adjustments for multiple comparisons were made.

RESULTS

Twenty-nine of 30 patients completed the study (97%). Patients ranged in age from 23 to 72 years (mean age, 37.5 years). There were 24 female patients and 5 male patients. Most patients reported such significant previous sedation with cetirizine that they had to stop taking the medication (16/29 or 55%), could only take it at night (10/29 or 34%), or could only take half the usual dose (3/29 or 10%). All data points across the 6 questionnaires per patient equaled 522 individual data points, and there were only 10 missing data points due to errors of omission in filling out the questionnaires, so that 512 of 522 (98%) of the questionnaire items were completed. One patient in the cetirizine arm of the study stopped taking the drug 1 day early because of excess reported sedation (and filled out the relevant questionnaire on day 6 rather than day 7), and an additional patient had to lengthen 2 washout periods (resetting each 5-day washout period back to day 0) after having 2 separate food allergy reactions.

In an initial qualitative comparison, using the ESS scores, 11 patients ranked the cetirizine arm as the most sedating, 6 patients ranked the levocetirizine arm as the most sedating, and 6 patients ranked the placebo arm as the

most sedating (the remainders ranked ≥ 1 of these equally). Using the Likert scale scores, 11 patients ranked the cetirizine arm as the most sedating, 5 patients ranked the levocetirizine arm as the most sedating, and 3 patients ranked the placebo arm as the most sedating (the remainder ranked ≥ 1 of these equally).

Sedation as measured by the ESS was not significantly different between the levocetirizine group (mean [SD] ESS score, 6.69 [4.05]) and the cetirizine group (mean [SD] ESS score, 7.48 [5.31]) ($P = .52$) (Fig 1). Similarly, sedation as measured by the Likert score was not significantly different between the levocetirizine group (mean [SD], 3.07 [1.92]) and the cetirizine group (mean [SD], 3.54 [2.17]) ($P = .42$) (Fig 2).

When we performed a subgroup analysis of the 16 patients who had reported such significant sedation with cetirizine that they were unable to tolerate continuing it, we also failed to find a significant difference in sedation between the cetirizine (mean score, 7.29) and levocetirizine (mean score, 6.86) groups as measured by the ESS ($P = .78$).

In addition, we failed to find a significant difference in sedation between the cetirizine (mean score, 3.86) and the levocetirizine (mean score, 3.0) groups as measured by the Likert scale ($P = .31$). The single patient who stopped taking cetirizine did so after day 6 of the cetirizine arm, and for this arm of the study she had a high ESS score (15) and a high Likert score (7). In comparison, her ESS and Likert scores during the levocetirizine arm were 13 and 3, respectively, whereas her ESS and Likert scores during the placebo arm were 12 and 5, respectively.

We failed to find any significant difference in efficacy as determined by the TRSS between levocetirizine (mean [SD], 3.14 [2.67]) and cetirizine (mean [SD], 2.67 [2.44]) ($P = .45$) (Fig 3). In comparison with placebo, the TRSS for cetirizine (mean [SD], 2.67 [2.44]) was significantly different from placebo (mean [SD], 4.41 [3.76]) ($P = .03$); however, the mean (SD) TRSS for levocetirizine (3.14 [2.67]) was not significantly

Table 2. Comparison of Outcomes During Washout Periods

Scale	No. of nonmissing values	Lower quartile/median/upper quartile (mean $\pm$ SD)			
		Washout 1 (n = 29)	Washout 3 (n = 29)	Washout 5 (n = 29)	Combined (n = 87)
ESS	85	2.00/6.00/8.00 (5.55 $\pm$ 3.55)	2.00/4.50/7.00 (4.89 $\pm$ 3.48)	2.00/3.00/6.25 (4.43 $\pm$ 2.95)	2.00/4.00/7.00 (4.96 $\pm$ 3.33)
Likert	84	1.00/2.00/3.00 (2.31 $\pm$ 1.47)	1.00/2.00/3.00 (2.04 $\pm$ 1.06)	1.00/2.00/2.25 (2.18 $\pm$ 1.39)	1.00/2.00/3.00 (2.18 $\pm$ 1.31)
TFSS	85	3.00/5.00/6.00 (4.59 $\pm$ 2.53)	2.00/4.50/7.00 (4.64 $\pm$ 2.80)	2.00/6.00/10.00 (5.93 $\pm$ 4.06)	2.00/5.00/7.00 (5.05 $\pm$ 3.22)

Abbreviations: ESS, Epworth Sleepiness Scale; TFSS, total 4-symptom scale.

Table 1. (Continued) Comparison of Outcomes Across Drugs

<i>P</i> value		
Cetirizine vs placebo	Levocetirizine vs placebo	Cetirizine vs levocetirizine
.27	.80	.52
.14	.54	.42
.03	.11	.45

different from placebo ($P = .11$). Table 1 summarizes the results of each of the 3 outcomes for each medication period.

We also analyzed whether each outcome was significantly different between each pair of washout periods (periods 1, 3, and 5 of the study). The distribution of TRSS was significantly different between washout periods 1 and 5 ($P = .04$) and between washout periods 3 and 5 ($P = .03$). However, sedation as measured by both the ESS and the Likert scale was not significantly different between any of the washout periods ($P > .05$ for all) (Table 2).

DISCUSSION

Of patients with a history of perceived moderate to severe sedation with cetirizine even to the point of being unable to tolerate cetirizine at all, most were able to tolerate levocetirizine based on our pilot study. However, this controlled trial also suggests that many of these patients would tolerate cetirizine if given in a masked manner (which is not practical in actual clinical practice). We had hoped to recruit patients who had experienced at least moderate sedation with cetirizine. Enrolled patients reported “significant sedation or somnolence” with cetirizine, many (16/29) to the point that they had to stop taking cetirizine and the others to the point that they could only take a reduced dose or take it only at night. Yet when patients took cetirizine in a masked manner, they rated their average sedation only as 3.54 on the 9-point Likert scale, and levocetirizine was rated an average of 3.07, with 3 indicating mildly sedating and 5 indicating moderately sedating. Even after performing the subgroup analysis of the 16 patients who could not tolerate taking cetirizine before this study, we found no significant differences in the mean sedation scores between the cetirizine and levocetirizine groups on either the ESS or the Likert scale. This finding implied that patient history of needing to stop cetirizine use because of sedation did not correlate with findings in this study. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine. In patients with a history of severe sedation with cetirizine, we do not know

whether levocetirizine would be less sedating. It is a weakness of this study that although we anticipated enrolling many patients unable to tolerate cetirizine, most of our patients were able to tolerate both cetirizine and levocetirizine (when given in a masked manner).

That this randomized, double-blind, placebo-controlled trial showed that levocetirizine was neither less sedating nor more effective than cetirizine might be in part due to the small sample size, especially in regard to the ESS, and thus the study may have been underpowered to detect a small but true difference. The ESS was included as a measure that had been used in previous studies and thus had some known performance characteristics; however, it may be less ideal at discriminating sedation induced by different antihistamines. Most studies examining the adverse effects of antihistamines have used objective ratings, such as psychomotor performance tasks. Few have used subjective ratings; those studies that have used subjective ratings typically use a 10-cm-long visual analog scale similar to the line analogue rating scale.^{17,18} We know of only one other study comparing sedation between cetirizine and levocetirizine (using both subjective and objective measures): a 4-day crossover study that showed no difference in subjective sedation with either medication compared with placebo.¹⁸

Sedation as measured by both the ESS score and the Likert scale was lower during the levocetirizine arm than in the cetirizine arm but not significantly so. The mean ESS scores were 4.96 for the combined washout period, 6.14 for the placebo period, 6.69 for the levocetirizine period, and 7.48 for the cetirizine period. Similarly, there was a parallel finding in the mean Likert scores across these periods: 2.18 for the combined washout period, 2.80 for the placebo period, 3.07 for the levocetirizine period, and 3.54 for the cetirizine period. These trends indicate the internal validity of using the measures that we did in the current study and the placebo effect. Similarly, the TRSS of 2.67 for the cetirizine period, 3.14 for the levocetirizine period, 4.41 for the placebo period, and 5.05 for the combined washout period suggest the internal validity of the measures and the presence of the placebo effect.

Table 2. (Continued) Comparison of Outcomes During Washout Periods

<i>P</i> value		
Washout 1 vs 3	Washout 1 vs 5	Washout 3 vs 5
.09	.07	.25
.72	.84	.47
.70	.04	.03

It is possible that the small differences in sedation between the groups with the large variation in responses as indicated by the relatively large standard deviations of the differences above may have obscured a true difference. We did not find levocetirizine to be significantly more effective (as measured by TRSS) than placebo, which also suggests that this study was underpowered because other large randomized trials have shown levocetirizine to be more effective than placebo.⁸ Furthermore, the particular patient population in this study had experienced significant sedation with cetirizine, so the generalizability of this study is limited to that particular clinical scenario because patients naive to both medications may indeed find levocetirizine less sedating and/or more effective than cetirizine. Patients naive to both medications were not included in this study because it would have necessitated a much larger sample size to detect a difference. Furthermore, this study addresses a somewhat different clinical scenario (ie, whether there is sufficient rationale to switch patients who report sedation with cetirizine to levocetirizine).

On the basis of these results, patients who had reported prior moderate to severe sedation with cetirizine appeared able to tolerate both levocetirizine and cetirizine with only mild sedation (albeit in a masked manner). The difference in sedation between levocetirizine and cetirizine was not significant; however, this may have been because the study was underpowered. In a post hoc analysis, we were underpowered to detect a 2-point difference in the ESS scores given the unexpectedly large standard deviation of the difference between the cetirizine and levocetirizine groups (which was 5.74). These results suggest that one viable clinical option for patients who have experienced significant sedation with cetirizine may be to offer them levocetirizine. However, the study also suggests that some may actually tolerate cetirizine again if it is given in a masked manner (an interesting finding but clinically impractical).

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