
A comparison of the effect of diphenhydramine and desloratadine on vigilance and cognitive function during treatment of ragweed-induced allergic rhinitis

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Background: Decrements in cognitive performance are associated with the use of sedating antihistamines. Most, but not all, second-generation antihistamines have been found to be nonsedating.

Objective: To examine the central nervous system (CNS) profile of a new second-generation antihistamine, desloratadine.

Methods: Subjects with ragweed-induced allergic rhinitis (aged 18–60 years) who demonstrated a predetermined severity of symptoms after priming with ragweed pollen in the Environmental Exposure Unit were randomized to receive a single dose of desloratadine, 5 mg; diphenhydramine, 50 mg; or placebo. A comprehensive battery of repeatable, automated neuropsychological tests was administered to subjects before treatment (symptomatic baseline) and 90 minutes after taking study medication.

Results: Both desloratadine ($P = .04$) and diphenhydramine ($P < .01$) alleviated the symptoms of allergic rhinitis compared with placebo, but treatment with diphenhydramine was associated with clinically meaningful decrements on all vigilance parameters ($P < .05$ for desloratadine-diphenhydramine contrasts). Also, subjects treated with diphenhydramine performed significantly worse than subjects given desloratadine or placebo across all cognitive domains evaluated. Most effect sizes for the mean desloratadine and diphenhydramine differences were between 0.4 and 0.8 (moderate to high). Stanford Sleepiness Scale scores also indicated significantly more somnolence with diphenhydramine vs desloratadine or placebo ($P < .001$). There were no significant differences on any of the cognitive parameters between subjects treated with desloratadine and those given placebo.

Conclusions: Desloratadine improved ragweed-induced allergic rhinitis symptoms without adversely affecting performance. Diphenhydramine improved allergic rhinitis symptoms but caused significant decrements in vigilance and cognitive functioning. Thus, efficacy of antihistamine treatment must be balanced against the associated effects on CNS functioning.

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INTRODUCTION

Seasonal allergic rhinitis (SAR) is characterized by inflammation of the nasal mucous membranes, with resultant nasal discharge, itching, sneezing, and congestion. Ocular symptoms may also be present. It is estimated that SAR affects up to 36 million people in the United States alone, and the expectation is of increased incidence in the future.¹ Recent studies have revealed significant economic impact of SAR and its treatment.^{2–5} As an example, a 1997 study estimated that the total annual medication cost (including prescription and nonprescription medications) associated with the treatment of SAR was \$2.4 billion, with an additional \$1.1 billion

spent on patient consultations with physicians.⁴ SAR symptoms also interfered with daily activities at home and school, decreasing productivity and increasing cost associated with the illness. The economic consequences of SAR have been described in terms of lost time at work (ie, sick days), suboptimal efficiency while performing one's job at work,^{2,3} employees taking time off to care for dependents with SAR, and workplace injuries related to SAR or its treatment with sedating medications.⁶ Since workers from all classifications of jobs experience SAR,⁷ there are significant financial and productivity losses across all sectors of the economy.

A main focus of research on decreased safety and productivity associated with SAR has been the negative side effects related to treatment with over-the-counter, first-generation antihistamines. These medications penetrate the blood-brain barrier, resulting in depressive effects on the central nervous system (CNS), including somnolence.⁸ Their use has been linked to decreased productivity in the workplace,⁹ impaired ability to safely operate a motor vehicle,^{10–12} and inefficient learning in the classroom.¹³ Studies suggest that these detrimental effects are related to cognitive impairment caused by these drugs.¹⁴ Specifically, sedating antihistamines have been associated consistently with decrements in vigilance (sus-

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tained attention)^{15,16} and with decreased divided attention,^{15,16} mental processing speed,^{16,17} reaction time,^{16,18} visual acuity,¹⁹ and short-term memory.²⁰ These performance characteristics have been described as important for adequate productivity, safety, and workplace efficiency²¹ and thus may at least partly underlie the negative economic consequences of SAR.

Most of the second-generation antihistamines penetrate poorly into the CNS and are associated with significantly reduced CNS effects compared with sedating antihistamines.^{12,16,22} Research indicates that treatment of SAR symptoms with non-sedating antihistamines actually leads to improved self-reported vigilance.²³ In a head-to-head comparison, diphenhydramine (a first-generation antihistamine) led to decreased vigilance, divided attention, and working memory, but loratadine (a second-generation antihistamine) did not.¹⁶ Not all second-generation antihistamines are equal in terms of their sedative properties. For example, the research on cetirizine, a second-generation antihistamine, is inconsistent. Some studies have indicated that cetirizine does not have sedative properties, whereas others have found adverse CNS effects for subjects taking the medication.^{24,25} The apparent differences in sedative properties of second-generation antihistamines is reason to examine their cognitive profiles.

Desloratadine, the active metabolite of loratadine and a newly derived, second-generation antihistamine, has recently become available for the treatment of allergic rhinitis in the United States. Research indicates that desloratadine is an effective treatment for allergic rhinitis.^{26–28} Since desloratadine-injected rats do not demonstrate sedation or impaired psychomotor functioning,²⁹ the antihistamine does not appear to cross the blood-brain barrier. Similarly, research in humans has shown that desloratadine does not have a negative impact on psychomotor performance and does not impair driving ability.^{30,31} The purpose of the current investigation was to objectively measure CNS effects of desloratadine on vigilance and cognitive functioning in humans. A computerized test battery used to evaluate vigilance and cognitive functioning was administered to ragweed-sensitive subjects in the Environmental Exposure Unit (EEU). The EEU is an effective model that has been used extensively to evaluate the onset of action and efficacy of antihistamines, nasal corticosteroids, and other investigational medications in the treatment of allergic rhinitis.³² It provides controlled antigen delivery for the production and maintenance of allergic

symptoms in susceptible individuals and, therefore, is an ideal setting to evaluate measures of vigilance and cognitive functioning where these can be effectively monitored. This controlled environment eliminates the confounding variables associated with traditional multicenter and park studies. Therefore, the impact of the allergic state and allergic medications can be reliably determined.

METHODS

Study Design

An investigational review board approved the study protocol, and the research was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained before enrollment. This was a double-blind, placebo-controlled, parallel-group, single-center study. Although a crossover design was considered, it was determined that a parallel group study addressed the hypotheses in a satisfactory manner. A crossover study would have added expense and time without increasing the power or validity of the study design.

Subjects were screened to ensure that they met criteria for study entry (see “Subjects” section) and then were primed to ragweed pollen in the EEU. Subjects were then randomized to 1 of 3 treatment groups (diphenhydramine, 50 mg; desloratadine, 5 mg; or placebo; Fig 1). The 2 medications and the placebo were overencapsulated so that all appeared identical. To minimize outdoor ragweed pollen exposure, data were collected during the (ragweed) off-season (summer 2000 and winter 2001) in the EEU. Since the goal of the research was to determine how treating symptomatic subjects with different medications affected cognitive functioning, it was essential that baseline evaluations occurred while subjects were experiencing allergy symptoms in the EEU. Thus, subjects in the study were not premedicated.

All subjects underwent 5 training sessions to familiarize themselves with the computerized performance battery and thus minimize practice effects during the symptomatic and treatment assessments. Subjects then attended priming sessions (1–6 sessions) where they were exposed to ragweed pollen in the EEU for up to 3 hours or until they reached a predetermined level of SAR symptoms (see *Symptom Evaluation*). Allergic subjects develop symptoms in a reproducible

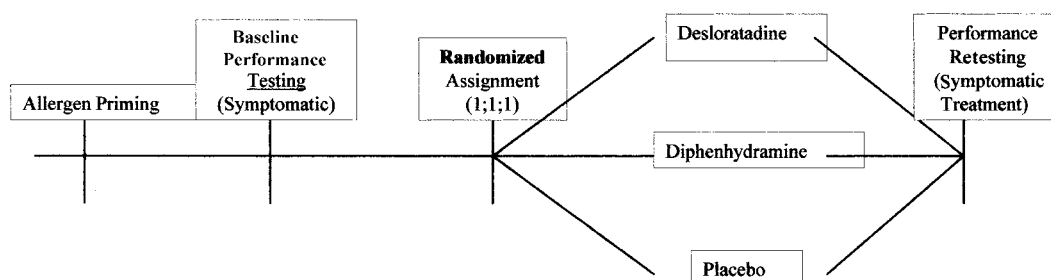


Figure 1. Study diagram.

manner following repeated exposure to pollen in the EEU.³² Subject response usually escalates, and this increase in reactivity is recognized as the priming effect.³³ Subjects then returned to the EEU to undergo symptomatic baseline performance testing. This allowed the level of vigilance and cognitive functioning for subjects experiencing SAR symptoms (before treatment) to be determined. After 1 week, subjects returned for the comparative treatment visit. All subjects were exposed again to ragweed in the EEU until they became sufficiently symptomatic, after which study medications were administered. All subjects then repeated the vigilance and cognitive performance battery at 1.5 hours after study medication. The amount of time between EEU exposure and testing was not statistically different at baseline or after taking medication. Immediately after completion of the performance battery, symptom status was reassessed and subjects rated globally the response of their SAR symptoms to the treatment they were given. Also, self-report questionnaires assessing subjective levels of sedation and perception of performance were completed. To control for potential effects of diurnal variables, all subjects completed performance testing at the same time of day on each of the testing days.

Subjects

Potential subjects with a minimum 2-year history of ragweed-induced SAR were screened. Unless performed within the previous 12 months, skin prick testing was performed to confirm ragweed sensitivity; wheals were measured after 15 minutes. Subjects were eligible if the resulting wheal following skin prick was at least 3 mm in diameter greater than the wheal for saline control. Subjects were required to meet the following criteria: age of 18 to 60 years, good general physical health, not color blind, not pregnant or breast-feeding, and a negative urine screen result for drugs of abuse.

Subjects were excluded from the study if they had a history of or current presentation of frequent, clinically significant sinusitis or chronic purulent postnasal drip; rhinitis medicamentosa; upper respiratory tract or sinus infection that required antibiotic therapy within 14 days of baseline performance testing or a viral upper respiratory tract infection within 7 days of baseline performance testing; nasal structural abnormalities that significantly interfere with nasal air flow; presence of asthma, unless controlled by as-needed inhaled β_2 -agonists (≤ 2 days per week); and use of immunotherapy, unless on a stable maintenance schedule. Subjects were not permitted to use investigational medications, corticosteroids, mast cell stabilizers, antihistamines, anticholinergics, leukotriene inhibitors, CNS depressants, theophylline, decongestants, tricyclic or tetracyclic antidepressants, or anorexigenic agents or cerebral stimulants within appropriate washout periods. Subjects with a history of perennial allergies could be enrolled as long as they were asymptomatic at the time of enrollment. Subjects were not permitted to ingest caffeine following breakfast on performance testing days. Subjects were also asked to maintain a regular sleep schedule, including a 10 PM to midnight bedtime, throughout the study.

Symptom Evaluation

Symptom severity status was evaluated via subject self-report. Subjects rated 8 individual nasal and nonnasal SAR signs and symptoms (Table 1). All subjects were required to have a total symptom severity score (TSS) of 10 or higher, a total nasal symptom score (TNSS) of 6 or higher, and a total nonnasal symptom score (TNNSS) of 4 or higher at the completion of the priming phase, at the symptomatic baseline evaluation, and on the treatment day before the dispensing of the study medication. Symptoms were again recorded by subjects after completion of the performance battery.

Vigilance and Cognitive Function Test Battery

The selection of tests and grouping of functions for this study are identical to the prior investigation on the burden of allergic rhinitis alone.³⁴ Assessment of vigilance and cognitive functioning was established through the completion of an easily repeatable, 45-minute computerized test battery (Table 2). A panel of experts on vigilance, sedation, SAR, and ability measurement had selected the specific measures included in the battery. Based on the consensus of these experts and prior research indicating that sedating antihistamines have their greatest adverse impact on vigilance,^{16,25} a measure of vigilance (Kay Continuous Performance Test [KCPT]) was designated the primary end point. Since prior research has also revealed that sedating antihistamines negatively affect various domains of cognitive functioning,¹⁶ measures designed to tap a wide range of cognitive abilities, such as working memory, reasoning, calculations, and psychomotor functioning, were included. Each measure included parameters sensitive to decrements in response time and information processing efficiency often associated with the use of sedating antihistamines.³⁵ All measures were required to have multiple alternate forms (ie, different but equivalent stimuli for each subsequent administration) and were computer administered. This makes the battery less susceptible to practice effects and thus more suitable for repeated measures in a large trial.

The tests selected for the study have been shown previously to have adequate validity and reliability as well as real-world significance and sensitivity to sedation and mild degrees of brain dysfunction.³⁶⁻³⁸ Descriptions of these tests can be found in a review article by Kane and Kay³⁹ and in prior research on the cognitive effects of sedating antihistamines.¹⁶

Table 1. Evaluated Signs and Symptoms of Seasonal Allergic Rhinitis*

Nasal	Nonnasal
Rhinorrhea	Itching/burning eyes
Nasal stuffiness/congestion	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears or palate

* Severity graded as 0 = none, 1 = mild (clearly present but minimal awareness, easily tolerated), 2 = moderate (definite awareness, bothersome but tolerable), or 3 = severe (hard to tolerate).

Table 2. Tests Used, Task Requirements, and Parameters Analyzed

Test	Task Requirement	Parameters Analyzed*
	Primary measure (vigilance)	
Key Continuous Performance Test ³⁶	Series of different symbols presented consecutively on screen for 10 minutes; subject required to tap key only when specified symbol is presented	Accuracy, omission errors, commission errors, response time
	Secondary measures	
ANAM Running Memory CPT ³⁷	Series of numbers presented rapidly and consecutively on screen for 10 minutes; subject required to determine whether current number is same or different from previous number	Accuracy, throughput, response time
ANAM Logical Reasoning ³⁷	Subject required to determine whether order of symbols (eg, #, &, \$) is accurately described by an accompanying statement	Accuracy, throughput, response time
ANAM Math Processing ³⁷	Subject required to determine whether math problems (each including both addition and subtraction) sum to greater or less than 5	Accuracy, throughput, response time
ANAM Digit Sequence Comparison Test ³⁷	Subject required to determine whether a sequence of digits matches a sequence presented on the prior screen	Accuracy, throughput, response time
ANAM Matching-to-Sample with Delay ³⁷	Visual grid with specified pattern appears on screen; after 5-second delay, subject required to choose grid with matching pattern to first from 2 similar grids	Accuracy, throughput, response time
CogScreen Digit Symbol Coding ³⁶	Subject required to match a series of symbols to a series of numbers as instructed by an on-screen key	Accuracy, throughput
CogScreen Digit Symbol Coding Delay ³⁶	After 20 minutes, subjects required to accurately match numbers with symbols as per the original Digit Symbol Coding key	Accuracy
CogScreen Visual Sequence Comparison Test ³⁶	Subjects required to quickly judge whether 2 numeric sequences presented on screen simultaneously are identical	Accuracy, throughput, response time
CogScreen Pathfinder ³⁶	Subject required to sequence series of numbers presented out of order on screen, then a series of letters; finally, subject required to alternate sequence between numbers and letters (combined condition)	Accuracy, throughput, response time, coordination (deviation from center of number or letter)
CogScreen Shifting Attention Test ³⁶	Subject required to choose correct response from multiple choices based on specified rule (arrow color, arrow direction, border color)	Accuracy, throughput, response time
CogScreen Dual Task Test ³⁶	Subject required to perform visual tracking task simultaneously with a working memory task (determining whether current number matches previous number)	Accuracy, throughput, speed (previous no. task); tracking errors, tracking boundary hits (tracking task)

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; CPT, Continuous Performance Test.

* Throughput score is a function of response time and accuracy; response time measured in milliseconds.

Cognitive Domains: Grouping of Tests

Given the large number of tests and parameters to be analyzed, tests were grouped a priori based on cognitive function for the purpose of interpretation. Since a number of the performance measures recommended for the current study were also used in prior antihistamine research¹⁶ and the factor analytic structure had been used to analyze those results, this same process was used as the initial template for collapsing the data into clinically meaningful groupings in this study. Information on construct

validity from the CogScreen and Automated Neuropsychological Assessment Metrics (ANAM) test manual^{36,37} and factor analytic studies conducted using ANAM and traditional neuropsychological measures^{40,41} were also used to determine the final test groupings. Finally, to confirm the appropriateness and goodness of fit of the test groupings, a correlation matrix of all test parameters was created and analyzed. As noted, past research^{16,25} has indicated consistent effects of sedating antihistamines on vigilance. Thus, this domain was designated as a significant area

of interest. The remaining 4 domains evaluated were working memory, psychomotor speed, reasoning/computation, and divided attention. Definitions of these domains and associated tests can be found in Table 3.

Statistical Analyses

All performance test parameters and allergic rhinitis symptom data were analyzed as continuous variables. Analysis of treatment efficacy was based on change in signs and symptom severity scores just before dosing on the treatment day (10:00 AM) and the posttreatment performance evaluation (1:00 PM). An analysis of covariance (ANCOVA) model containing the baseline evaluation as the covariate was used to control for baseline differences in symptom scores. As for cognitive performance, subjects in the 3 groups (placebo, desloratadine, and diphenhydramine) were compared with regard to change from the symptomatic baseline to the treatment testing session. Difference score comparisons among the 3 groups were based on an ANCOVA model with the baseline evaluation as the covariate. Self-report questionnaires that assessed subjective level of seda-

tion and perception of performance on the cognitive battery were analyzed using the Cochran-Mantel-Haenszel test stratified by baseline. All statistical tests were 2-sided and performed at the .05 level of significance. To help determine whether cognitive decrements associated with SAR treatment were related more to physical symptoms (ie, poor vision due to tearing or watery eyes) or actual changes in CNS functioning (ie, sedation, mental slowing), change scores (between the symptomatic baseline and posttreatment testing) for all cognitive measures were correlated with changes in SAR composite symptom scores from before to after treatment (TSS, TNSS, TNNSS). All statistical analyses were completed using the SAS statistical software package (SAS Institute Inc, Cary, NC).

RESULTS

Demographics

A total of 248 subjects were randomized to receive medication: diphenhydramine, 84; desloratadine, 81; and placebo, 83. Due to computer-related technical difficulty and subjects

Table 3. Cognitive Domains, Definitions, and Associated Tests

Cognitive Domain	Definition	Associated Test(s)*
Primary Domain		
Vigilance	Sustained attention over time. It is the ability to maintain a certain level of arousal or attention while engaged in a monotonous or repetitive task. An example would be driving on a boring road for several hours while maintaining alertness or maintaining accurate performance on an assembly line.	Kay Continuous Performance Test, all parameters
Secondary Domains		
Working memory	The ability to solve problems in one's head. Requires one to acquire information, perform some type of mental operation on the information, and produce a correct response. The "memory" part of this definition is the ability to hold in one's head all elements of the problem (and various subsolutions of the problem) while performing the mental operation. A good example is keeping a running tally of a cumulative sequence of numbers.	ANAM Running Memory CPT ANAM Digit Set Comparison ANAM Matching-to-sample CogScreen Shifting Attention Test
Psychomotor speed	The speed and accuracy with which one can complete tasks that rely on hand-eye coordination. It does not just entail speed of mental processing or speed of motor functioning. Rather, it is a combination of the two. It looks at how well a person can perform a task that involves both motor processing and efficient thinking. A good example is typing.	CogScreen Symbol Digit Coding CogScreen Visual Sequence Comparison CogScreen Pathfinder (number and letter conditions)
Reasoning/computation	This domain can be thought of as including tasks that require higher cognitive functioning. This is defined as the ability to reason, problem solve, or perform complex mental calculations.	ANAM Logical Reasoning ANAM Math
Divided attention	The ability to divide one's attention between 2 simultaneous tasks or to alternate attention back and forth between 2 tasks. A good example is talking on the telephone while cooking dinner.	CogScreen Dual Task Test CogScreen Pathfinder (Combined Condition)

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; CPT, Continuous Performance Test.

* Due to a computer malfunction, CogScreen Symbol Digit Coding Delay was not administered properly (ie, two thirds of the items were not administered). Therefore, this test was not included in data analysis or interpretation.

not meeting the respective requirements for SAR symptoms (ie, too few symptoms and/or inadequate severity) on the symptomatic baseline testing day, 44 subjects were excluded from testing. These excluded subjects were distributed among the 3 treatment groups, thus limiting systematic bias. Consequently, 204 subjects were randomized to treatment and received diphenhydramine (69), desloratadine (68), or placebo (67). Demographic data of the 204 subjects completing the study as per the initial protocol are presented in Table 4; the groups were well balanced at randomization in both the intent-to-treat and per-protocol populations. There were no statistically significant differences between the groups in any of the demographic variables analyzed. Similarly, there were no statistical differences in symptom scores among subjects in different groups or among subjects in the same group at the baseline visit.

At the baseline (symptomatic) testing session, between-group (diphenhydramine vs desloratadine) differences were found for 4 of the 60 test parameters (ANAM Logical Reasoning test, response time, $P = .02$; CogScreen Combined Pathfinder, coordination, $P = .047$; CogScreen Dual Task Test [alone], tracking errors, $P = .04$, and boundary hits, $P = .046$). As noted, adjustments for these baseline differences were made using an ANCOVA model with the baseline evaluation as the covariate.

Effects of Antihistamines on Vigilance

Subjects taking diphenhydramine performed significantly worse on all parameters of vigilance compared with subjects taking either desloratadine or placebo (Figs 2 through 5). This effect was most pronounced when diphenhydramine was compared with desloratadine. Greater differences were measured between diphenhydramine and desloratadine than between diphenhydramine and placebo.

Effect sizes of score differences between desloratadine and diphenhydramine (in SD units) for the KCPT parameters most sensitive to lapses in vigilance were in the moderate-to-high range (omission errors, 0.63; accuracy, 0.67; correct hits, 0.58). These effect sizes represent clinically meaningful⁴² differences in change scores between subjects taking desloratadine and subjects taking diphenhydramine. Al-

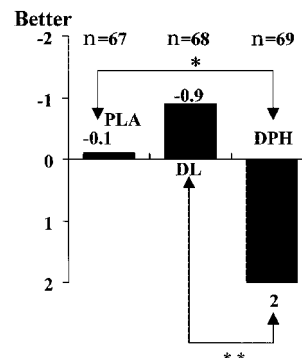


Figure 2. Change from baseline in number of Kay Continuous Performance Test omission errors. PLA indicates placebo; DL, desloratadine; and DPH, diphenhydramine. * $P < .05$. ** $P < .01$.

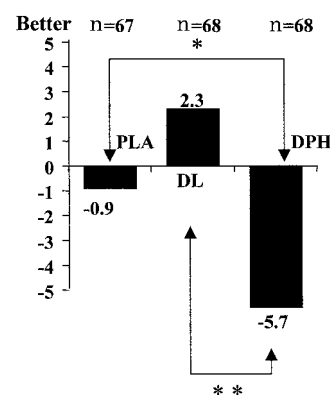


Figure 3. Change from baseline in Kay Continuous Performance Test accuracy percentage. PLA indicates placebo; DL, desloratadine; and DPH, diphenhydramine. * $P < .05$. ** $P < .01$.

though there were slight mean differences favoring the desloratadine group compared with the placebo group on the KCPT parameters, these differences were not statistically significant (omission errors, $P = .31$; accuracy, $P = .42$; correct hits, $P = .27$; response time, $P = .10$).

Table 4. Demographic and Baseline Characteristics (All Randomized Subjects)*

Characteristic	Placebo Group		Desloratadine Group		Diphenhydramine Group	
	Intent to treat (n = 83)	Per protocol group at final testing (n = 67)	Intent to treat (n = 81)	Per protocol group at final testing (n = 68)	Intent to treat (n = 84)	Per protocol group at final testing (n = 69)
Mean age, y	33	31.8	31	37.1	34	35.0
Male, No. (%)	36	46.3	35	42.6	37	42.0
Race, No. (%)						
White	81	97	78	95.6	78	94.2
Black	0	0	0	0	0	0
Asian	0	0	2	2.9	4	4.3
Hispanic	0	0	0	0	1	1.4
Other	2	3	1	1.5	1	0

* None of the mean group differences met the .05 level of significance.

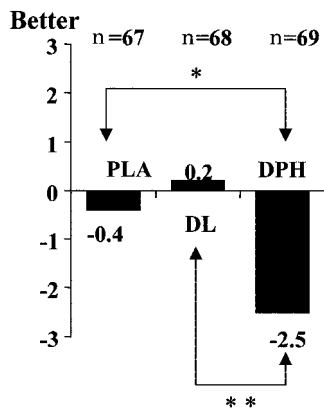


Figure 4. Change from baseline in Kay Continuous Performance Test number of correct hits. PLA indicates placebo; DL, desloratadine; and DPH, diphenhydramine. * $P < .05$. ** $P < .01$.

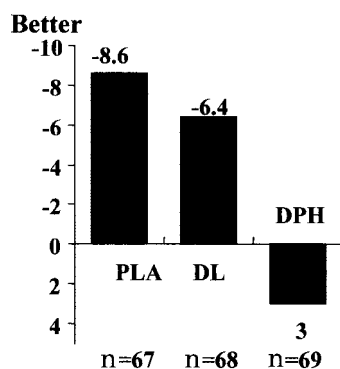


Figure 5. Change from baseline in Kay Continuous Performance Test response time in milliseconds. PLA indicates placebo; DL, desloratadine; and DPH, diphenhydramine. DL-DPH comparison $P < .01$.

Effects of Antihistamines on Performance on Broader Cognitive Battery

As summarized in Table 5, subjects taking diphenhydramine performed significantly worse on most measures across all other cognitive domains evaluated (working memory, psychomotor speed, reasoning/computation, divided attention) compared with subjects taking either desloratadine or placebo. The range for effect sizes of mean differences between desloratadine and diphenhydramine was between 0.12 and 0.90 SD, with the majority between 0.4 and 0.8 SD (moderate to high). These findings thus represent clinically meaningful impacts on performance-related abilities when diphenhydramine is compared with desloratadine. The greatest impacts were observed in the performance-related domains of vigilance and working memory. There were no statistically significant differences between subjects taking placebo and those taking desloratadine on any of the measures of cognitive functioning. Although there were slight mean differences favoring either the desloratadine group or the placebo group on certain parameters, these differences were not statistically significant.

Self-reported Sedation Related to Medication

Subjects taking diphenhydramine self-reported significantly worse functioning on the performance battery ($P < .001$) compared with subjects taking desloratadine or placebo. Furthermore, on the Stanford Sleepiness Scale, subjects in the diphenhydramine group reported a significantly greater degree of sedation ($P < .001$) following the completion of the test battery than subjects taking either desloratadine or placebo (Figure 6).

On the remaining questionnaire items, subjects taking diphenhydramine reported being significantly more drowsy and lethargic and less clear-headed, quick-witted, attentive, coordinated, and proficient than subjects taking desloratadine or placebo. Of note, compared with subjects in the diphenhydramine group, subjects in the desloratadine group reported being significantly more clear-headed ($P = .05$) and less drowsy ($P = .046$) than those in the placebo group.

Signs and Symptoms: Medication Efficacy

There were no significant baseline differences in symptom severity among the 3 treatment groups with regard to TSS, TNSS, and TNNSS. Both desloratadine and diphenhydramine produced statistically significant reductions in TSS ($P < .001$ and $P < .04$, respectively) and TNSS ($P < .001$ and $P < .046$, respectively) compared with placebo at the completion of the test battery (time after dose, approximately 3 hours). There was also a significant improvement in nonnasal symptoms (TNNSS) for subjects taking diphenhydramine ($P < .001$) and a marginal improvement for desloratadine ($P < .06$) compared with subjects taking placebo. Finally, self-reported global therapeutic response was found to be significantly better in subjects taking either desloratadine ($P = .03$) or diphenhydramine ($P < .001$) compared with placebo.

Correlations Between Cognitive Performance and SAR Symptoms

For subjects in the diphenhydramine and desloratadine groups, there were no statistically significant correlations between any of the composite SAR symptom change scores and cognitive performance change scores ($P > .35$ for all correlations). Hence, symptom improvement was not associated with improved cognitive performance.

DISCUSSION

The use of first-generation, sedating antihistamines (eg, diphenhydramine) has been linked to decrements in vigilance and impaired cognitive and psychomotor functioning.^{16–20} Although most second-generation antihistamines do not appear to affect cognition, there are some, such as cetirizine, that have been found to affect psychomotor functioning and are recognized to have sedative properties at recommended doses in 13% of patients compared with 6% taking placebo.²⁵ The objective of this study was to compare to what extent desloratadine, a new second-generation antihistamine, and diphenhydramine differentially affect an individual's vigilance and cognitive performance, since desloratadine has not previously been evaluated for these parameters. The findings

Table 5. Secondary End Points: Means and Effect Sizes for Significant Analysis of Variance Results*

Cognitive domain	Neuropsychological test	Mean (SD)			P Value (desloratadine-diphenhydramine contrast)*	Effect size†
		Desloratadine	Diphenhydramine	Placebo		
Working memory	ANAM Running Memory CPT					
	Accuracy	0.4 (4.8)	−4.3 (11.1)	0.1 (8.1)	<.001	0.55
	Throughput‡	3.8 (12.6)	−10.0 (18.1)	1.2 (16.5)	<.001	0.88
	Response time§	−10.3 (35.4)	32.2 (56.8)	−1.1 (33.9)	<.001	0.90
	ANAM Digit Set Comparison					
	Accuracy	1.6 (8.2)	−4.6 (11.7)	−0.6 (9.9)	<.001	0.61
	Throughput	0.3 (8.2)	−5.1 (11.9)	1.0 (9.9)	<.001	0.53
	Response time	−10.6 (152.3)	77.5 (188.7)	−2.3 (197.9)	<.001	0.51
	ANAM Matching-to-Sample					
	Accuracy	0.3 (10.6)	−4.4 (15.1)	1.2 (9.4)	<.001	0.36
	Throughput	0.6 (9.3)	−2.5 (9.6)	4.0 (10.8)	.02	0.34
	Response time	−26.9 (330.2)	181.8 (762.8)	−112.7 (344.3)	.003	0.35
	CogScreen Shifting Attention Test					
	Instruction condition (accuracy)	−0.1 (3.9)	−2.6 (6.6)	0.1 (5.9)	.006	0.47
Psychomotor speed	Instruction condition (throughput)	0.0 (8.8)	−5.8 (11.8)	12.0 (12.3)	<.001	0.56
	Instruction condition (response time)	0.1 (79)	53 (130)	−7 (116)	.005	0.48
	CogScreen Symbol Digit Coding					
	Accuracy	0.9 (4.6)	−0.2 (3.4)	0.7 (4.5)	.008	0.28
Reasoning/computation	Throughput	2.1 (5.2)	0.6 (6.9)	3.2 (6.4)	.008	0.25
	CogScreen Number Pathfinder					
	Throughput	1.9 (8.8)	−1.0 (10.8)	2.9 (12.6)	.03	0.29
	ANAM Logical Reasoning					
Divided attention	Throughput	1.1 (4.6)	1.1 (7.1)	−1.0 (6.6)	.008	0.37
	ANAM Math					
	Accuracy	−1.0 (7.0)	−3.8 (9.1)	−0.7 (15.0)	.04	0.35
	CogScreen Combined Pathfinder					
	Accuracy	−.2 (4.0)	−2.4 (6.5)	0.6 (5.4)	<.001	0.42
	Throughput	−2.7 (11.3)	−5.4 (14.1)	0.2 (12.8)	<.001	0.21
	Response time	21 (133)	45 (240)	−0.23 (231)	.01	0.12

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; CPT, Continuous Performance Test.

* Only reported for parameters in which omnibus *P* value was significant at the .05 level. In addition, contrast analysis indicated that placebo subjects' performance was significantly better (at the .05 level) than diphenhydramine subjects' performance for all measures included in chart. For all measures presented in chart, there were no statistically significant differences between desloratadine and placebo subjects when contrasts were performed.

† Effect sizes represent difference in change scores between desloratadine and diphenhydramine.

‡ Throughput is a composite measure of efficiency (correct responses per minute); higher scores indicate better performance.

§ Response time measured in milliseconds; higher scores indicate worse performance.

of this study show that the decrements in vigilance and cognitive functioning (ie, working memory, psychomotor speed, reasoning/computation, divided attention) associated with diphenhydramine treatment are not observed with desloratadine treatment.

No significant correlations were identified between any of the composite allergic rhinitis symptom change scores and cognitive performance change scores. This indicates that antihistamine-related symptom improvement was not associated with improved cognitive performance. Thus, although traditionally the means of assessing the effectiveness of SAR treatments have been limited to the 4 nasal and 4 nonnasal signs and symptoms, this method may not be sufficient be-

cause it does not provide information about vigilance and cognitive functioning. From a clinical perspective, the negative impact of treatment with a sedating antihistamine on performance-related abilities can be substantial and cannot be predicted from knowledge of the signs and symptoms of SAR. In fact, treatment with sedating antihistamines appears to be associated with a distinct profile of cognitive decrements, including reduced vigilance and deterioration in a number of domains of cognitive functioning (ie, working memory, divided attention, reasoning/computation, and psychomotor speed). This is consistent with research on other conditions in which the cause of cognitive decline is not a focal lesion but rather a more global process affecting the

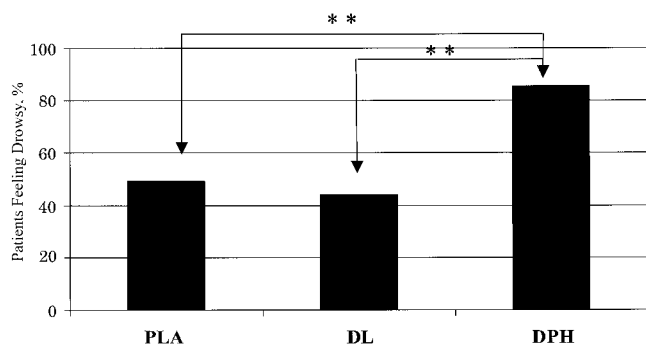


Figure 6. Percentage of patients feeling drowsy (Stanford Sleepiness Scale score 3). PLA indicates placebo; DL, desloratadine; and DPH, diphenhydramine. ** $P < .01$.

whole brain.^{43–45} SAR treatment with desloratadine, a newly available nonsedating antihistamine, was efficacious with regard to the traditional metric of assessing SAR severity (ie, signs and symptoms) without significantly affecting cognitive performance.

The measurement of vigilance and cognitive functioning, although not a substitute for the traditional signs and symptoms, provides an objective measure of functional impact not available from signs and symptoms alone. Prior research has indicated that performance on neurocognitive measures accurately predicts real-world performance on common tasks in a variety of settings (ie, work, home, school).^{46–51} As such, it is possible to make some conjectures about these data that help shed some light on the real-world implications of using a sedating antihistamine compared with a nonsedating antihistamine. Regarding vigilance, the decrement of 0.63 SD on the KCPT in subjects taking diphenhydramine indicates the omission of response to 3 of the target symbols during the testing interval (10 minutes). This finding may potentially be extrapolated over several hours or an entire day because sustained attention is necessary to complete even the most basic work-, school-, and home-related tasks.⁴³ This 0.63-SD change could thus represent an increase of 144 more omission errors throughout an 8-hour workday. Such omission errors affect worker safety, productivity, and personal security.

Similarly, hypotheses can be made about how decrements in the other cognitive domains associated with diphenhydramine (but not desloratadine) may have important implications for performance at work, school, and home. Specifically, decreased speed and accuracy on measures of working memory and reasoning/computation suggest deterioration in the ability to perform tasks that require mathematics or problem solving (eg, computer programming, classroom performance). It could also affect one's ability to integrate information from multiple sources to ensure safety and accurate completion of tasks (eg, air traffic control). The decrement in divided attention has implications for safety while driving or operating heavy machinery. It could also affect a manager's ability to simultaneously oversee multiple aspects of a particular project. Finally, even subtle decreases in psychomotor

speed can have a great impact on safety. O'Hanlon and colleagues^{12,52,53} found that use of sedating antihistamines generally results in an increased reaction time of 0.1 to 0.2 second. Although this may seem like a small change without much clinical significance, a decrement of 0.1 second translates into an increased stopping distance of 20 ft in a truck, which could determine whether or not a collision occurs. This observation of the real-life dangers associated with "small" changes such as these has been influential in the creation of laws that make it illegal to drive while impaired from a sedating antihistamine in 32 states in the United States. The differences between first- and second-generation antihistamines relative to CNS penetration and somnolence and psychomotor speed has also led to the recommendation (before the development of even newer agents) that SAR patients who operate heavy machinery (eg, a motor vehicle) use nonsedating, second-generation antihistamines to treat their symptoms.⁵⁴

It is important to recognize the limitations of this study. First, the study analyzed performance-related impacts after an initial, single dose of either diphenhydramine or desloratadine. Results from the study indicate that, for those subjects taking diphenhydramine as needed (ie, sporadically), the potential for sedation and decrements in cognitive functioning is high. Current findings, however, do not touch on steady-state dosing. Future studies should examine as needed vs steady-state dosing of diphenhydramine. Prior findings³⁴ suggest that SAR, independent of treatment, is associated with decreased cognitive functioning. Thus, it may be the case that those treated with a nonsedating antihistamine over time (ie, steady state) will perform better than those not treated at all for SAR. Steady-state performance trials will also help determine efficacy differences between first- and second-generation antihistamines. This would enable clinicians to incorporate data regarding both efficacy and performance into their treatment decisions. Second, future research is needed to establish more rigorously the link between treatment-related neurocognitive decrements and the effect of treatment on safety and productivity in the real world. Finally, diphenhydramine is approved for the treatment of allergies at both 25- and 50-mg doses. Thus, future studies are needed to determine whether findings are similar for patients using the 25-mg dose of diphenhydramine.

CONCLUSION

In this study, treatment with desloratadine led to improvement of allergic rhinitis symptoms. Although treatment of SAR with diphenhydramine, a sedating antihistamine, also led to improvement in symptoms, it came at the expense of intact CNS functioning (ie, vigilance and cognition). Although further research is needed to better characterize the impact on cognitive functioning of the various antihistamines used to treat SAR, these findings support the use of new second-generation antihistamines in the workplace, while driving, and in other situations where vigilance and cognition are important.

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