Cognition and Allergy: CLEAR Study Results

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ABSTRACT

Background: Research indicates that seasonal allergic rhinitis (SAR) can cause cognitive decrements. Though a number of first-generation antihistamines have sedative properties, many second-generation antihistamines treat SAR without iatrogenic sedation. Thus, treatment of SAR with nonsedating antihistamines should lead to improved cognitive functioning via both symptom alleviation and lack of sedative effects. Most research on the central nervous system (CNS) effects of antihistamines has been with healthy controls. The objective of the CLEAR (Cognitive Effects of Loratadine: Effect on Allergy Response) study was to determine whether treating symptomatic SAR with loratadine, a nonsedating antihistamine, helps symptomatic patients perform as well as those without allergies on cognitive measures.

Methods: This was a multicenter, placebo-controlled, double-blind, parallel-group study. Subjects were randomized to 3 groups. The first (n=101) included normal controls. The other 2 included symptomatic SAR sufferers randomized to loratadine (n=100) or placebo (n=100) for 5 days. A cognitive battery was administered at baseline and treatment days 1, 3, and 5.

Results: Subjects receiving loratadine performed as well as those without allergies on all cognitive measures by day 5. In contrast, throughout the study, placebo-treated SAR sufferers performed significantly worse than those without allergies on most measures of attention, alertness, and focus ($P<0.05$).

Conclusions: SAR adversely affects cognitive functioning. CLEAR study results show that treating SAR with loratadine, a nonsedating antihistamine, enables allergy sufferers to perform as well as those without allergies. This is likely related to both symptom alleviation and lack of medication-related sedation.

INTRODUCTION

For many years, allergic rhinitis (AR) has been thought of as solely a physical condition. Although common physical symptoms (eg, runny nose, itchy eyes) clearly have a major effect on allergy sufferers, recent research has indicated that the impact of AR on these individuals' lives is much larger than many suspect. Both adults[1] and children[2] with AR have been shown to experience cognitive difficulties, such as decreased ability to focus, decrements in alertness, and a decline in sustained attention and vigilance. To further compound this problem, some antihistamines sold over the counter are known to be sedating. It has been demonstrated that allergy sufferers taking diphenhydramine, a sedating first-generation antihistamine, experience significant decrements in cognitive function that are caused by both their condition and the treatment itself.[3,5] Given the importance of efficient cognitive processing at work and school, impaired cognition due to AR and some AR treatments may affect productivity and performance in these arenas.[6,7]

Recently available second-generation antihistamines (eg, loratadine) provide relief from allergy symptoms, yet are far less likely to cross the blood-brain barrier and therefore do not cause sedation when used at recommended doses. Indeed, loratadine has been shown to alleviate the physical symptoms of AR and does not contribute to cognitive impairment.[8]

These findings and principles were the impetus for the CLEAR study (Cognitive Effects of Loratadine: Effect on Allergy Response), in which we sought to determine whether treatment with a nonsedating antihistamine would help AR sufferers function cognitively similarly to those without allergies.

OBJECTIVES

1. To determine whether AR sufferers treated with a nonsedating antihistamine (ie, loratadine) perform better on cognitive tasks than those who are not treated (ie, taking a placebo).
2. To determine whether treating allergies with a nonsedating antihistamine (ie, loratadine) helps AR sufferers function as if they do not have allergies.

METHODOLOGY

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. For purposes of this study, loratadine (administered as CLARITIN® 10 mg qd) was used. This was because loratadine is the only second-generation antihistamine available over the counter. Thus, findings may be applied to a much larger proportion of the AR population than if a prescription medication were used.

The study included 3 groups of subjects ≥18 years of age. The first (n=101) was a normal control group (subjects without allergies). The other 2 groups were composed of subjects with seasonal AR who were experiencing allergy symptoms at the time of study enrollment. These individuals were randomized to receive either loratadine 10 mg once daily (n=100) or placebo once daily (n=100) for 5 days.

A battery of repeatable, automated neuropsychological tests (Automated Neuropsychological Assessment Matrices: ANAM) (Table 1) was administered to subjects with AR prior to treatment (baseline) and 90 minutes after dosing with study medication on Days 1, 3, and 5. Subjects in the normal control group were tested according to the same schedule. The test battery was heavily weighted toward measures of alertness and focus.

Statistical Analysis

There were 2 main thrusts of the statistical analysis. The first was to determine whether cognitive performance was better in those AR sufferers treated with the nonsedating antihistamine, loratadine, as compared with placebo. The second, and main, analysis was conducted to determine whether treatment with loratadine, compared with placebo, allowed AR sufferers to function as well as those without allergies. For the first analysis, the change in cognitive function scores from baseline to 1.5 hours post-treatment was the primary variable. The 2 treatment groups were compared in an analysis of covariance model that included treatment and baseline differences. Comparisons were made separately for Days 1, 3, and 5. If any measure was found to significantly deviate from the required normal distribution assumption, then the Wilcoxon rank sum test was used as a nonparametric alternative. In a second analysis, absolute cognitive function scores were compared at baseline and at each of the 3 test days for all 3 groups using a repeated-measures ANOVA design.

RESULTS

Subject demographics and baseline characteristics were similar among the 3 groups (Table 2).

Comparison vs Placebo

On a number of measures of working memory and complex attention, there were significant differences and trends indicating that allergy sufferers receiving loratadine performed better than those receiving placebo (Table 3).

Comparison vs Normals

When allergy sufferers were compared with non-allergy sufferers, it was found that, by Day 5, untreated AR sufferers (ie, those receiving placebo) performed significantly worse than non-allergy sufferers on several measures of working memory, concentration, and visual discrimination ($P<0.05$ for all comparisons) (Table 4 and Figures 1 and 2).

In contrast, loratadine allowed allergy sufferers to perform similarly to those without allergies on all measures of attention. By Day 5 of the study, there was no statistical difference between AR sufferers receiving loratadine and those without allergies on measures of working memory, concentration and sustained attention, and visual discrimination and analysis (Table 4 and Figures 1 and 2).

Figure 1: ANAM Mathematical Processing: A test of mathematical computation and working memory

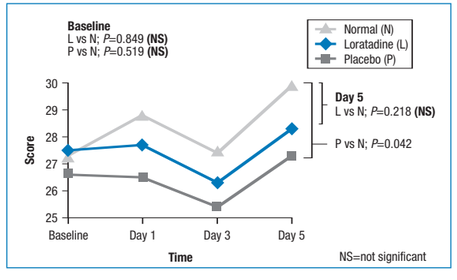


Table 1: Measures of attention, alertness, and focus

Cognitive Performance Measure	Cognitive Function	Test Description
Automated Neuropsychological Assessment Matrices (ANAM) Running Memory CPT (Continuous Performance Test)	Sustained Attention, Working Memory, Resistance to Interference	Requires sustained attention in response to a stimulus on a computer screen during a forced-pace, rapid task. Numbers are presented on the screen, and the user must press a specified key indicating whether the number is the same or different from the previous number.[9]
ANAM Mathematical Processing	Mathematical Computation, Working Memory	Math problems are presented on the screen; the answer must be figured out, then the user must decide if the answer is > or < the number 5.[9]
ANAM Logical Reasoning Test	Abstract Reasoning, Problem Solving, Verbal Functioning	This is a linguistic task requiring the ability to apply rules of syntax and grammar; a symbol pair (eg, "#&" or "&#") is presented, and the user must respond logically to statements describing the order of the symbols on the screen.[9]
ANAM Digit Set Comparison	Perceptual Sensitivity, Working Memory	A string of digits ranging from 2 to 10 is presented on the screen; the string then disappears, and a second set is presented. The user must decide if the 2 strings are the same and respond by clicking a button on the mouse.[9]
ANAM Matching-to-Sample, With Delay	Working Memory, Perceptual Sensitivity	The user must respond correctly to stimuli that correspond in some way to a sample stimulus. First, a 12-cell matrix is presented with a number of cells shaded; the user is then presented with 2 matrices and must choose which one matches the sample matrix.[9]
ANAM Procedural Reaction Time	Choice Reaction Time	Numbers (2, 3, 5, or 6) are presented on the screen one at a time. If the number is a 2 or a 3, the user clicks the left mouse key. If the number is a 5 or 6, the user clicks the right mouse key.[10]
ANAM Digit Symbol Coding	Psychomotor Speed, Working Memory	Nine symbol/number pairs are displayed in a key at the top of the screen. The user must determine whether symbol/number pairs displayed in rapid succession in a sample box at the bottom of the screen represent accurate pairings as per the key at the top of the screen.[9]

Table 2: Subject demographics and baseline characteristics

Characteristic		Loratadine (n=100)	Placebo (n=100)	Normals (n=101)	*P* value
Sex, n (%)	Male	38 (38)	28 (28)	41 (40.6)	0.144
	Female	62 (62)	72 (72)	60 (59.4)	
Race, n (%)	Caucasian	77 (77)	72 (72)	85 (84.2)	0.107
	Black	10 (10)	14 (14)	12 (11.9)	
	Hispanic	13 (13)	14 (14)	4 (4)	
	Asian	0 (0)	0 (0)	0 (0)	
	Other	0 (0)	0 (0)	0 (0)	
Age (yrs)	Mean (SD)	36.5 (11.36)	37.6 (10.89)	33.9 (11.16)	0.056
Height (cm)	Mean (SD)	168.6 (9.41)	168.3 (8.07)	170.5 (9.45)	0.170
Weight (kg)	Mean (SD)	83.0 (22.47)	83.7 (22.36)	83.7 (23.50)	0.967
Temperature (ºC)	Mean (SD)	36.67 (0.398)	36.63 (0.398)	36.60 (0.295)	0.419
Pulse (beats/min)	Mean (SD)	72.6 (8.99)	73.5 (9.46)	72.8 (9.98)	0.762
Respiration rate (breaths/min)	Mean (SD)	16.3 (2.32)	16.5 (2.21)	16.7 (2.47)	0.457
Systolic BP (mm Hg)	Mean (SD)	118.0 (12.16)	118.6 (12.74)	120.0 (15.28)	0.552
Diastolic BP (mm Hg)	Mean (SD)	75.2 (8.23)	75.8 (8.89)	77.1 (9.54)	0.313

Table 3: Differences in cognitive function change scores (ie, postdose – baseline) between loratadine and placebo

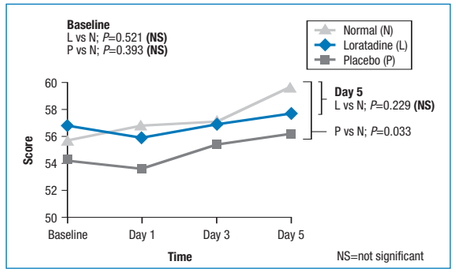
Test Name/Parameter	Day	Loratadine Mean Score (SD)	Placebo Mean Score (SD)	*P* value
Math Processing/Response Time	1	-33.5 (428.67)	81.4 (301.40)	0.05
Math Processing/Response Time	3	7.2 (378.58)	164.8 (311.42)	0.003
Math Processing/Response Time	5	-66.9 (403.17)	35.4 (296.28)	0.079 (trend)
Digit Set Comparison L7/Response Time	1	-55.9 (314.81)	-2.2 (385.79)	0.057 (trend)
Digit Set Comparison L7/Response Time	5	-159.2 (411.91)	-100.2 (366.64)	0.043
Digit Set Comparison L8/Response Time	5	-187.9 (417.96)	-119 (402.09)	0.036
Digit Set Comparison Combined/Throughput	5	6 (11.26)	3.2 (9.55)	0.058 (trend)

Table 4: *P* values for the comparisons with normals at Day 5

Measure	Cognitive Function	Loratadine vs Normals	Placebo vs Normals
ANAM Running Memory CPT, Throughput	Sustained Attention, Working Memory, Resistance to Interference	0.187	0.024
ANAM Digit Set Comparison	Perceptual Sensitivity, Working Memory	0.168	0.008

ANAM=Automated Neuropsychological Assessment Matrices CPT=Continuous Performance Test

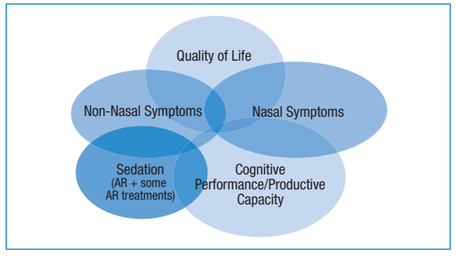
Figure 2: ANAM Digit Symbol Coding: A test of psychomotor speed and working memory



CONCLUSIONS

- When left untreated, AR causes sedation and decrements in cognitive function, alertness, and focus
- The first-generation antihistamine, diphenhydramine, when used to treat AR, causes sedation and adversely impacts cognitive function
- Results from the CLEAR study show that treatment of AR with loratadine (CLARITIN®), a nonsedating second-generation antihistamine, can help allergy sufferers perform as if they did not have allergies. On the other hand, not treating allergies causes AR sufferers to perform worse than those without allergies on measures of attention
- CLEAR study findings have significant implications for AR sufferers in terms of quality of life and maintaining optimal performance on tasks requiring alertness and focused attention. These include:
  - Operating machinery
  - Performing office work
  - Driving
  - Paying attention in school
- Given the effects of AR on many aspects of quality of life, it is important to think beyond only the signs, symptoms, and efficacy of treatment. Rather, physicians and health care providers must broaden their focus in assessing the effects of allergies and treatments on patients (Figure 3).

Figure 3. A broader view of AR symptomatology



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