

The effects of antihistamines on cognition and performance

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Allergic diseases are responsible for substantially more disability than is generally realized. Allergic rhinitis alone results in 3.5 million lost workdays and 2 million missed school days in the United States each year. Comorbid conditions such as asthma and sinusitis can be disabling as well, resulting each year in more than 10 million missed school days and more than 73 million days of restricted activity, respectively. Antihistamines continue to be the mainstay of treatment for allergic disorders. In the case of the first-generation antihistamines, however, the treatment may well be worse than the disease. Although these agents are effective H₁-receptor antagonists, they are also highly lipophilic and readily cross the blood-brain barrier, causing considerable sedation. The second-generation agents are more lipophobic and possess different ionic charges than the first-generation antihistamines. As a result, they are far less likely to cross the blood-brain barrier and, for that reason, cause little if any sedation. In a recent comparative trial, subjects who were treated with the first-generation agent diphenhydramine were found to have significant performance deficits on tests of divided attention, working memory, vigilance, and speed. By contrast, subjects who were treated with the second-generation antihistamine loratadine performed as well as subjects who were treated with placebo. The sedative effects of the first-generation agents persist well into the next day and thus can potentially interfere with daytime performance and safety even when taken the night before. It is therefore recommended that patients whose occupations require vigilance, divided attention, or concentration receive only second-generation antihistamines. (*J Allergy Clin Immunol* 2000;105:S622-7.)

Key words: Allergic rhinitis, antihistamines, functional capacity

Allergic diseases are extraordinarily common in the United States, affecting more than 20% of the population.¹ A recent *Time* magazine article reported that up to 40% of the population may experience allergic rhinitis. Allergic rhinitis alone affects more than 40 million individuals in the United States each year.¹

The everyday misery caused by the sneezing, wheezing, coughing, and itching that accompany allergic diseases is well known. The strong link between allergic rhinitis and such serious conditions as asthma and sinusitis is also understood with increasing clarity.¹ What is generally less recognized is the enormous impact that these conditions have on functional capacity in both adults and children.

Abbreviations used

CI: Confidence interval
OR: Odds ratio

Part of this functional disability is caused by the disease itself. Allergic rhinitis, for example, is known to cause substantial systemic symptoms in addition to its localized symptoms (eg, weakness, malaise, irritability, fatigue, headache, and anorexia).¹ Decrements in cognitive functioning and learning capacity have been demonstrated to occur even in atopic adults and children² independent of medication. It is primarily these systemic effects of allergic rhinitis and the resulting diminished functional capacity that are responsible for the 3.5 million workdays and 2 million school days that are lost each year to allergic rhinitis alone.¹ Corollary conditions such as asthma and sinusitis exact a substantial toll as well; asthma accounts for more than 10 million missed school days each year, and sinusitis results in more than 73 million days of restricted activity annually.¹

Importantly, however, it is not only the disease itself that diminishes mood, energy, and cognitive functioning, but it is also the treatment of the condition. In the United States, sedating antihistamines continue to be the mainstay of treatment for allergic disorders, as they have been for the past 5 decades. Antihistamines are typically categorized as either first-generation agents or second-generation agents (Table I). There are substantial differences between these two classes of antihistamines with respect to their impact on safety, performance, and mood.

EVOLUTION OF THE ANTIHISTAMINES

The first-generation antihistamines were discovered approximately 60 years ago and have been available for at least the last 40 years. These agents are highly potent competitive inhibitors for histamine, acting at the histamine H₁-receptor site on most target cells in the respiratory mucosa. However, these agents are characterized by ethylamine moieties, which make them highly lipophilic and hence easily able to penetrate the blood-brain barrier and occupy H₁-receptor sites in the brain, a large number of which are located on the frontal lobes and in the deep structures of the brain. In fact, positron emission tomography studies conducted by Yanai et al³ have demonstrated that the first-generation agents occupy approximately 75% of the H₁-receptor sites in the brain. The well-known central nervous system side effects of these agents (including fatigue, drowsiness, and performance impairment) are a result of this

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0091-6749/2000 \$12.00 + 0 1/0/106153

doi:10.1067/mai.2000.106153

TABLE I. Selected first- and second-generation oral antihistamines

	Onset of Action (h)	Sedative side effects	Possible cardiac side effects
First-generation antihistamines			
Brompheniramine (Dimetapp)	1	Yes	No
Chlorpheniramine maleate (Chlor-Trimeton)	1	Yes	No
Diphenhydramine hydrochloride (Benadryl)	1	Yes	No
Second-generation antihistamines			
Cetirizine (Zyrtec)	1-2	Yes	No
Fexofenadine (Allegra)	1-2	No	No
Fexofenadine/pseudoephedrine (Allegra-D, 12 hr)	1-2	No	No
Loratadine (Claritin)	1-2	No	No
Loratadine/Pseudoephedrine (Claritin-D, 12 h; Claritin-D, 24 h)	1-2	No	No

characteristic. Because of these side effects, the first-generation antihistamines are required to carry a precautionary statement that admonishes users against operating a car or dangerous machinery when taking these agents.

The second-generation antihistamines, which were introduced in the mid-1980s, were designed specifically with the goal of producing agents that would be as effective as the first-generation H_1 -receptor antagonists but without their sedative effects. Several variations on the original agents were introduced to accomplish this goal. The second-generation antihistamines are more lipophobic than their predecessors, and they possess a different ionic charge. In addition, they are made up of larger molecules than the first-generation agents. These 3 factors in combination appear to be what makes it substantially more difficult for these molecules to cross the blood-brain barrier. This is not to say that they do not do so at all; the second-generation agents are capable of passing through to the brain, but they do so to a far lesser extent. Yanai et al³ have shown that the second-generation agents occupy approximately 20% of H_1 -receptor sites in the brain, substantially fewer than do their first-generation predecessors. Furthermore, the level of cognitive dysfunction was shown to correlate with brain-receptor occupancy. Therefore, it is not surprising that the second-generation antihistamines are less sedating than the first-generation antihistamines and that specific agents, namely loratadine and fexofenadine, are not required to carry a warning for sedation and, in fact, exert virtually no sedating effects at their therapeutic dose.

EFFECTS OF SEDATING ANTIHISTAMINES ON RISK OF OCCUPATIONAL INJURIES

Recent research has shown that the warning labels for sedation that appear on the first-generation antihistamines are well deserved and, in fact, should be taken far more seriously than they generally are. In an effort to determine the effect of medication use on work-related injury, Gilmore et al⁴ at the Group Health Cooperative of Puget Sound of Seattle, Washington, conducted a medication-use review of 3394 members of their health maintenance organization

TABLE II. Adjusted ORs of sustaining a work-related injury by class of medication used

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Adapted from Gilmore TM, Alexander BH, Mueller BA, Rivara FP. Occupational injuries and medication use. *Am J Ind Med* 1996;30:234-9. Copyright 1996. Reprinted by permission of John Wiley & Sons, Inc.

who had sustained work-related injuries. These cases were compared with data from 2 uninjured matched control groups that were selected from the health maintenance organization membership. The investigators found that the individuals who had used sedating antihistamines had the highest increase in risk of injuries among all of the drug categories studied (including narcotic, nonnarcotic analgesic, antidepressant, sedative hypnotic, antibiotic, gastrointestinal medication, hypoglycemic, and antipsychotic).⁴ Antihistamine use was associated with an increased risk of every kind of injury studied, including open wounds and contusions (odds ratio [OR], 0.5; 95% confidence interval [CI], 11.9), burns (OR, 3.1; 95% CI, 1.0-9.7), and fractures (OR, 1.7; 95% CI, 0.9-3.3). The overall adjusted OR for sustaining a work-related injury was 1.5 for antihistamine users (95% CI, 1.1-1.9) compared with 0.9 for individuals taking narcotics (95% CI, 0.7-1.1; Table II).⁴

EFFECTS OF SEDATING ANTIHISTAMINES ON DRIVING PERFORMANCE

The effects of antihistamines on driving capabilities have been well studied in the Netherlands where "over-

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FIG 1. Factual knowledge scores (mean $\pm$ SE) in children with no allergy (NOR) versus children with allergy who were treated with the nonsedating antihistamine loratadine (LOR), placebo (PLA), or the sedating antihistamine diphenhydramine (DIP). (Modified with permission from Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6. Copyright ACAAI.)

the-road" studies (as opposed to laboratory-simulation driving studies) are often conducted. In one such study, O'Hanlon⁵ compared the tendency to weave while driving in subjects who were being treated with the first-generation antihistamine triprolidine or the second-generation antihistamines terfenadine or loratadine. He found that the subjects who were being treated with either of the second-generation antihistamines demonstrated no increase in the amount of weaving compared with baseline at either 1 or 3 hours after medication ingestion. By contrast, individuals who had taken triprolidine evidenced as much driving impairment as would be expected in an individual with a 0.05 mg/dL blood alcohol level.⁵

These results are consistent with those from an epidemiologic study of automobile fatalities conducted in Ontario, Canada.⁶ This study demonstrated that drivers who were killed in automobile accidents attributed to their own error were 1.5 times more likely to have been using a first-generation antihistamine than were drivers not responsible for the accident in which they were killed.⁶ As a consequence of data like these, 32 states and the District of Columbia have enacted laws against driving while impaired as a result of taking sedating medications, including over-the-counter first-generation antihistamines.

EFFECTS OF ANTIHISTAMINES ON SCHOOL PERFORMANCE IN ATOPIC CHILDREN

Children are also vulnerable to the performance-impairing effects of first-generation antihistamines. Vuurman et al² studied learning performance in a group of 52 primary-school children with a history of seasonal allergic rhinitis. They compared the performance of these

children with that of a group of age-matched children with no allergies. The atopic children received one of three treatments before instruction: a sedating antihistamine (diphenhydramine), a nonsedating antihistamine (loratadine), or a placebo. All of the children returned 2 weeks later, after the allergy season was over, to take tests of their factual knowledge, conceptual knowledge, and ability to apply a learned strategy.

Analysis of the data demonstrated that the atopic children performed consistently less well on measures of factual knowledge ($P < .01$; Fig 1), conceptual knowledge ($P < .02$; Fig 2), and knowledge application ($P < .02$; Fig 3) than did the nonatopic children.² Among the atopic children, however, those treated with loratadine or placebo demonstrated better learning performance than did the diphenhydramine-treated students.² Thus, atopy itself tends to worsen learning capacity in children, and these decrements are exacerbated by treatment with sedating antihistamines. A single-dose treatment with a nonsedating antihistamine was not sufficient to overcome the effects of atopy.

EFFECTS OF FIRST- VERSUS SECOND-GENERATION ANTIHISTAMINES ON SEDATION, COGNITION, MOOD, AND PSYCHOMOTOR PERFORMANCE

In an effort to determine whether the second-generation antihistamines are less likely to cause decrements in the areas of mood, cognition, and sleepiness than their predecessors, our group tested these variables in 98 healthy volunteers who were randomly assigned in double-blind fashion to receive loratadine ($n = 33$), diphenhydramine ($n = 32$), or placebo ($n = 33$).⁷ At baseline, on

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FIG 2. Conceptual knowledge scores (mean $\pm$ SE) in children with no allergy (*NOR*) versus children with allergy who were treated with the nonsedating antihistamine loratadine (*LOR*), placebo (*PLA*), or the sedating antihistamine diphenhydramine (*DIP*). (Modified with permission from Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6. Copyright ACAAI.)

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FIG 3. Knowledge application scores (mean $\pm$ SE) in children with no allergy (*NOR*) versus children with allergy who were treated with the nonsedating antihistamine loratadine (*LOR*), placebo (*PLA*), or the sedating antihistamine diphenhydramine (*DIP*). (Modified with permission from Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6. Copyright ACAAI.)

day 1 after the administration of the initial dose and on days 3 and 5, these individuals underwent a comprehensive battery of psychometric tests designed specifically to mirror real-world tasks.

On day 1, diphenhydramine (50 mg) was found to have produced substantial adverse effects on divided attention, working memory, vigilance, and speed.⁷ By contrast, subjects being treated with loratadine (10 mg)

performed as well as subjects being treated with placebo. Similarly, on measures of mood, subjects being treated with diphenhydramine reported higher levels of fatigue ($P < .001$) and had lower levels of motivation ($P < .001$) than did subjects being treated with loratadine; they also rated the quality of their test performance as lower ($P < .001$) relative to subjects being treated with loratadine (Fig 4).⁷ Further, subjects being treated with diphenhy-

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FIG 4. Mean change from baseline in visual analog scale (VAS) ratings on day 1 for subjects who were treated with diphenhydramine, loratadine, and placebo. $P < .001$, loratadine versus diphenhydramine; $P < .001$, placebo versus diphenhydramine. (Adapted from Kay GG, Berman B, Mockoviak SH, Morris CE, Reeves D, Starbuck V, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 1997;157:2350-6. Copyright 1997, American Medical Association.)

dramine reported lower levels of activity. The subjects being treated with loratadine, by contrast, evidenced no differences from the subjects being treated with placebo. Although results from testing on days 3 and 5 showed some equilibration among the groups, subjects being treated with diphenhydramine continued to make substantially more tracking errors on tests of divided attention and reported greater fatigue.

Interestingly, in the diphenhydramine group, with those subjects who self-reported that they were not sedated ($n = 22$), performance on measures of divided attention, working memory, and vigilance was substantially impaired. Thus, individuals whose ability to function is compromised by first-generation antihistamines may lack awareness of their reduced level of functioning.

It should be noted that the performance deficits observed in this study are far from inconsequential. In fact, on measures of vigilance, the performance of subjects who were treated with diphenhydramine was approximately a full standard deviation worse than the performance of subjects who were treated with loratadine or placebo. Differences of this magnitude are interpreted by neuropsychologists as indicative of impaired brain function.⁸ Moreover, deficits on tests of attention and vigilance indicate an increased likelihood of errors in the performance of tedious but potentially hazardous tasks of daily living, such as driving an automobile. On similar cognitive tests, differences of the magnitude seen with diphenhydramine are similar to those noted after alcohol intoxication.

EFFECTS OF AN "AM/PM" ANTIHISTAMINE DOSING REGIMEN

The first-generation antihistamines clearly produce sedation and impair performance to a much greater extent than do the second-generation antihistamines.

However, because they are newer, the second-generation agents are associated with higher direct drug costs. Some physicians prescribe a regimen wherein over-the-counter sedating agents are taken at night and nonsedating prescription agents are taken during the day. The rationale behind this so-called "AM/PM dosing regimen" is that patients would "sleep through" the sedative effects of the first-generation agents with no aftereffects the next day.

To test the actual effect of such a regimen on daytime sleepiness and level of alertness, our group studied these variables in 29 healthy volunteers. Subjects were randomized, in double-blind fashion, to one of three parallel treatment groups: an evening dose of 12 mg of the first-generation agent chlorpheniramine plus a morning dose of 60 mg of the second-generation agent terfenadine ($n = 9$); an evening dose of 8 mg of chlorpheniramine plus a morning dose of 60 mg of terfenadine ($n = 9$), or a morning plus an evening placebo dose ($n = 11$).⁹

All subjects underwent the Multiple Sleep Latency Test (an objective physiologic measure of sleepiness) and the Stanford Sleepiness Scale (a measure of subjective sleepiness and alertness). Results from these tests demonstrated that subjects who had received the AM/PM dosing regimens had increased daytime sleepiness and reduced alertness. Subjects who had received evening doses of chlorpheniramine in combination with morning doses of terfenadine fell asleep more quickly during the next day and described themselves as less able to concentrate and less alert than did those subjects who had received placebo. Even after 4 days of the AM/PM regimen, a significantly higher proportion of subjects who were treated with 12 mg of chlorpheniramine had abnormal daytime sleepiness compared with the subjects treated with placebo ($P = .03$). Thus, it is clear that the central nervous system depressant effects of an evening dose of a first-generation antihistamine persist through the next day.⁹

CONCLUSIONS

The first-generation antihistamines negatively affect mood, sleepiness, alertness, and cognitive and psychomotor functioning in adults and children. As a result, these medications can interfere with performance and safety, even when taken the night before. Because patients are frequently unaware of the level to which their performance is impaired, they are likely to fail to use adequate caution in performing potentially dangerous activities, such as driving a car or operating heavy machinery, while under the influence of sedating antihistamines.

Adults who have jobs that demand divided attention, vigilance, and concentration are most likely to be adversely affected by the sedating antihistamines. Adverse effects are not limited to driving and operating dangerous machinery. Performance of clerical and monitoring jobs is also likely to be negatively affected. As a consequence, it is recommended that adults whose occupations demand divided attention, vigilance, or concentration receive nonsedating antihistamines in preference to sedating antihistamines, whenever possible. Children, too, should be treated with nonsedating antihistamines to avoid the adverse effects of the first-generation agents on learning capability.

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