Sedation and performance impairment of diphenhydramine and second-generation antihistamines: A meta-analysis

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Background: Antihistamines are among the most frequently used medications in the United States. Despite dramatically higher cost, second-generation antihistamines are replacing diphenhydramine because of the perception that they are not constrained by its sedating effects.
Objective: We sought to examine, through meta-analytic procedures, the collective evidence regarding the sedating and performance-impairing effects of diphenhydramine relative to placebo and second-generation antihistamines.
Methods: A search that began with the MEDLINE database was limited to those studies that included patients with atopic disease and control subjects, were blinded and randomized clinical trials, objectively examined alertness and psychomotor performance, reported means and variances, and were written in English. Information was systematically abstracted from the resulting 18 articles, and effect size was calculated.
Results: Diphenhydramine impaired performance relative to placebo control and second-generation antihistamines, including acrivastine, astemizole, cetirizine, fexofenadine, loratadine, and terfenadine. However, results were quite varied, the average sedating effect of diphenhydramine was modest, and in some instances results of tests of performance in the diphenhydramine group showed less sedation than in the control or second-generation antihistamine groups. A significant ($P < .05$) average effect size indicated a mild sedating effect caused by second-generation antihistamines in comparison with placebo.
Conclusion: The absence of a consistent finding of diphenhydramine-induced sedation is surprising given that most studies have been designed to increase the probability of this outcome, including administering a 50-mg dose. On the basis of this meta-analysis of performance-impairment trials, a clear and consistent distinction between sedating and nonsedating antihistamines does not exist. (J Allergy Clin Immunol 2003;111:770-6.)

Key words: *Allergic rhinitis, antihistamines, diphenhydramine, meta-analysis, sedation*

Allergic rhinitis affects 23.7 million Americans.[1] Because antihistamines are the first choice for treatment of allergic conditions, they are among the most frequently used medications in the United States,[2] with sales of prescription antihistamines increasing 16% in 2001 alone.[3] Use of first-generation antihistamines is widespread, largely because they are inexpensive and available over the counter. Prescriptions for second-generation antihistamines, marketed for their nonsedating benefits, have increased dramatically in recent years despite their markedly higher cost.

Abbreviations used
ES: Effect size
MeSH: Medical Subject Headings

Diphenhydramine is the most commonly used first-generation antihistamine. Its capacity for sedation is so widely recognized that it is frequently the verum control drug in studies seeking to show the relative nonsedating benefit of second-generation antihistamines, including cetirizine, loratadine, terfenadine, astemizole, fexofenadine, and acrivastine.[4] Studies of diphenhydramine largely document some sedative side effect, but results are inconsistent, and some studies find no sedation.

The purpose of this meta-analysis was to systematically search, compile, review, analyze, and critique the existing diphenhydramine research literature and perform statistical analysis on defined subsets of studies addressing sedation. This project thus examined the collective evidence regarding the sedating and performance-impairing effects of diphenhydramine relative to second-generation antihistamines to provide physicians and consumers with a clearer understanding of the relative risks associated with its use.

METHODS

Meta-analysis is an approach in which individual study outcomes are quantitatively combined to arrive at overall conclusions regarding a clearly specified body of research. The purposes of meta-analysis are to (1) increase statistical power for primary end points and subgroups, (2) resolve uncertainty when studies disagree, (3) improve estimates of treatment effectiveness, and (4) answer questions not posed at the start of individual trials.[5] To date, no meta-analytic review has specifically addressed the effects of diphenhydramine on psychomotor performance compared with placebo and second-generation antihistamines.

Selection of studies

A literature search for relevant diphenhydramine studies was executed by using the MEDLINE database. The source literature population of studies consisted of controlled clinical trials in peer-review journals. A comprehensive search was performed with a MEDLINE file dated from 1966 to identify studies for inclusion in

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this meta-analysis. The term "histamine h1 antagonists" and 34 specific generic names of first- and second-generation antihistamines were used in the MEDLINE database search, retrieving 25,894 citations. These were cross-indexed with the research areas related to alertness and psychomotor performance. These areas were examined to identify search terms in the Medical Subject Headings (MeSH terms). Terms such as "cognition disorders," "learning disorders," "psychomotor performance," "reaction time," "fatigue," "mental processes," "confusion," and "psychological tests" were exploded to include all conceptually narrower terms in the MeSH hierarchy. The truncated text word for the concept of sedation was used as well. This group of terms retrieved 1,112,254 citations. The crossed retrieval was then limited to human studies and to English-language studies, producing 2134 citations. These were limited to the MEDLINE publication type "randomized controlled trial," resulting in a retrieval of 455 citations. The same set was also limited to MeSH terms for supported research, yielding 404 citations. Combined, these sets produced a pool of 722 citations. Of these, only 125 contained the word "diphenhydramine." Abstracts were reviewed, and when the information was insufficient to determine eligibility, the full text was reviewed. Articles were rejected on the topics of psychiatric disorders and therapies (39), cancer (12), anesthesia (17), caffeine (4), dentistry (2), or ophthalmology (1). A final cause of rejection was the incomplete reporting of means and variance (35), leaving 15 articles. Three articles, the indexing of which did not match the extensive search criteria, were located in the bibliographies of reviewed articles. Eighteen articles met all inclusion criteria and were included in this meta-analytic study.[7-24] From these, 20 separate outcomes were evaluated (Table I).

Inclusion criteria

To qualify, studies included (1) atopic disease, even if patients were asymptomatic; (2) blinded, randomized designs that included a placebo group; (3) diphenhydramine as one of the drugs administered; (4) laboratory measures of sedation or psychomotor performance as outcomes; (5) appearance in an English-language journal indexed between January 1966 and January 2002; and (6) report of means and variances (SD or SE) allowing for the calculation of an effect size (ES). Although blinded drug conditions might introduce difficulty if encapsulation changes drug-absorption characteristics, the importance of blinding subjects during evaluation of potential sedation necessitated this inclusion criterion. All included studies from a single research group were examined to ensure that each study's data were collected independently of each other to avoid multiple publication biases. The most common causes of rejection from this meta-analysis were (1) focus on a nonatopic disease, (2) inclusion of anecdotal adverse reports without actual performance or sedation measures, and (3) failure to report a measure of variance (ie, SD).

Reported outcomes

Studies included in this meta-analysis had to report at least one of the 5 categories of sedation-performance measures most commonly encountered in the published literature:

1. Self-reported sleepiness. This measure included either a visual analog scale (consisting of a 100-mm line on which participants selected a point between 2 extremes from "very sleepy" to "very awake" best representing their degree of alertness) or the Stanford Sleepiness Scale (which allowed the subject to choose one of 5 statements reflecting similar degrees of alertness).[6]
2. Attention. Measures of attention included the CogScreen Dual Task Test,[10] Divided Attention Task,[28] Critical Flicker Fusion,[11,20] and Continuous Performance Test.[15]
3. Memory. Measures of memory included the Automated Neuropsychological Assessment Metrics Documentation Test, Running Memory Test,[10] Digit Symbol Substitution Test,[14] Buschke Selective Reminding Test,[15] Serial Digit Learning Test,[12,16] a computerized learning task,[21] and a classroom learning test.[7]
4. Reaction time. Reaction time was measured by means of computerized calculation of the time from presentation of a stimulus to the subject's response.
5. Eye-hand coordination. Included were measures of fine motor tracking,[11] symbol copying,[14] and fine motor speed.[12]
6. Evoked brain potentials. The P300 event-related potential measure is viewed as a direct, physiologic, central nervous system measure of sedation and is obtained by means of electroencephalographic recording of brain wave activity. This methodology was reported in 2 studies by one research group.[18,19]

Data abstraction

The following information was abstracted from each published article and coded and constituted the analytic data base: subject characteristics, including age, sex, race, height, weight, and illness characteristics; study design; drug type, dose, and delivery route; time lapse between dosing and psychometric measurement; type of measure and its outcome (mean and SD); and funding source (industry vs government; Table I). All data were independently abstracted by 2 investigators (BGB, ZVT) to avoid intercoder bias. Every coded item was reviewed to ensure accuracy and consistency, and disagreements were resolved by means of consensus.

Analysis

A protocol specifying the framework for this meta-analysis was written in advance of data collection. The primary outcome in this study was the difference in psychomotor performance between 2 treatment groups. For a given measure (eg, self-reported sleepiness and attention), an ES was calculated as follows: Δ_1 equals diphenhydramine minus placebo divided by pooled SDs (Fig 1, *A*); Δ_2 equals diphenhydramine minus second-generation antihistamines divided by pooled SDs (Fig 1, *B*); and Δ_3 equals second-generation antihistamines minus placebo divided by pooled SDs (Fig 1, *C*). This standardized ES represents the size of the average difference between 2 groups on one of the selected outcome measures.[26] Pooled outcomes were calculated by assigning weights equal to the inverse of the total variance for mean effects. The 95% CI is reported to provide the reader the likely range of values associated with each ES. By using this approach for calculating ES, scores greater than 0 indicated increased sedation of the indicated drug. Thus an ES of 1.00 would indicate that the average (or mean) subject in one group outperforms 84% of subjects in the other group (ie, 1 SD above the mean is the 84th percentile).

A random-effects model was used for all analyses because this approach collapses into a fixed-effects model in the absence of significant ES heterogeneity.[25,26] For categoric variables, subgroup analyses were performed by using ANOVA-like procedures for meta-analysis. The α level for a type I error was set at a *P* value of less than .05. Bonferroni adjustments were not made because of the increased likelihood of a type II error.

RESULTS

Diphenhydramine versus placebo

Diphenhydramine altered performance on measures believed to reflect the effects of sedation. When diphenhydramine was contrasted with placebo (Fig 1,

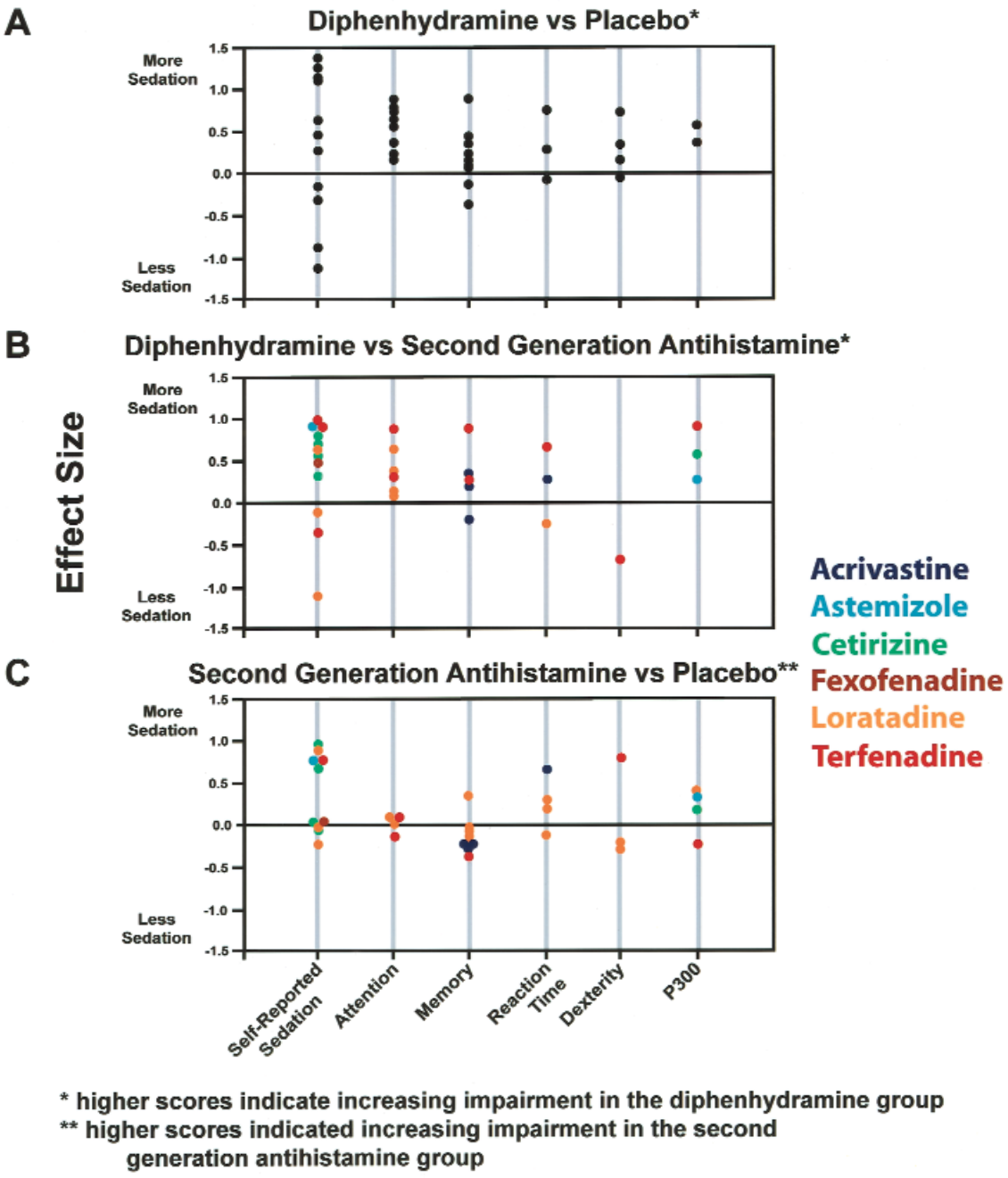

FIG 1. Sedation and performance impairment.

A), the mean ES across all 6 measures and all 18 studies was 0.36 (95% CI, 0.20-0.51; $P = .0001$). Although this showed a moderate overall sedation effect of diphenhydramine, results were distinctly variable across studies, and not all studies reported diphenhydramine sedation. Significant measure-specific ESs were found for attention (ES = 0.53; 95% CI, 0.36-0.71; $P = .0001$). The diphenhydramine-placebo ES did not reach statistical significance for measures of memory, reaction time, dexterity, or evoked brain potential measure, although it approached significance for self-report (ES = 0.41; 95% CI, –0.07 to 0.90; $P = .089$) and memory (95% CI, –0.01 to 0.33; $P = .051$). Because less than 5 ESs were available for pooling for measures of reaction time, dexterity, and evoked brain potential, these results were deemed insufficient to accurately assess whether the overall ES was significant. Available data suggest a small ES in the direction of diphenhydramine-induced impairment consistent with the overall findings (Fig 1, *A*).

TABLE I. Data abstraction format for key variables

Study	Age (y)	Disease	Funding	Design	N	Drug and dose	Performance measure
Bender et al, 2001	8-10	Atopic/ historical	Industry	Parallel groups	21	Diphenhydramine, 25 mg bid oral	Memory, reaction time
					21	Loratadine, 10 mg qd oral	
					21	Placebo	
Berlinger et al, 1982[8]	65-81	Normal	Government/ industry	Crossover	12	Diphenhydramine, 50 mg iv	Self-report
					12	Diphenhydramine, 50 mg oral	
					12	Placebo	
Carruthers et al, 1978[9]	26	Normal	Government	Crossover	6	Diphenhydramine, 50 mg iv	Self-report
					6	Diphenhydramine, 50 mg oral	
					6	Placebo	
Kay et al, 1997[10]	31	Normal	Industry	Parallel groups	33	Diphenhydramine, 50 mg oral	Self-report, memory
	31	Normal					
	32	Normal			32	Loratadine, 10 mg oral	
					33	Placebo	
Mattilla et al, 1986[11]	24	Normal	Not reported	Crossover	13	Diphenhydramine, 50 mg oral	Self-report, attention, dexterity
					13	Temelastine, 100 mg oral	
					13	Placebo	
Philpot et al, 1993[12]	Not reported	Normal	Not reported	Crossover	12	Diphenhydramine, 50 mg oral	
					12	Chlorpheniramine, 4 mg oral	
					12	Terfenadine, 60 mg oral	
					12	Placebo	
Ramaekers and O'Hanlon, 1994[13]	33	Normal	Not reported	Crossover	18	Diphenhydramine, 50 mg oral	Reaction time
					18	Terfenadine, 180 mg oral	
					18	Acrivastine, 24 mg oral	
					18	Placebo	
Roth et al, 1987[14]	29	Normal	Not reported	Crossover	16	Diphenhydramine, 50 mg oral	Attention, memory, reaction time, dexterity
					16	Loratadine, 10 mg oral	
					16	Loratadine, 40 mg oral	
					16	Placebo	
Sands et al, 1997[15]	71	Normal	Not reported	Crossover	30	Diphenhydramine, 50 mg oral	Attention, memory
					30	Diphenhydramine, 75 mg oral	
					30	Placebo	
Scavone et al, 1998[16]	30	Normal	Government	Crossover	20	Diphenhydramine, 25 mg oral	Memory
					20	Placebo	
Scavone et al, 1998[16]	67	Normal		Crossover	17	Diphenhydramine, 25 mg oral	Memory
					17	Placebo	
Schweitzer et al, 1994[17]	31	Atopic/ historical	Industry	Crossover	12	Diphenhydramine, 50 mg oral	Self-report
					12	Cetirizine, 10 mg oral	
					12	Placebo	

(continued on next page)

TABLE I. Continued

Study	Age (y)	Disease	Funding	Design	N	Drug and dose	Performance measure
Simons et al, 1995[18]	22.6	Normal	Industry	Crossover	20	Diphenhydramine, 50 mg oral	Self-report, P300
					20	Hydroxyzine, 50 mg oral	
					20	Cetirizine, 10 mg oral	
					20	Placebo	
Simons et al, 1996[19]	23.7	Normal	Industry	Crossover	15	Diphenhydramine, 50 mg oral	Self-report, P300
					15	Astemizole, 10 mg oral	
					15	Terfenadine, 60 mg oral	
					15	Loratadine, 10 mg oral	
					15	Cetirizine, 10 mg oral	
					15	Ketotifen, 2 mg oral	
					15	Placebo	
Tharion et al, 1994[20]	19.9	Normal	Not reported	Crossover	9	Diphenhydramine, 50 mg oral	Attention
					9	Terfenadine, 60 mg oral	
					9	Placebo, 80 mg oral	
Vuurman et al, 1996[21]	20	Atopic/active	Industry	Parallel groups	24	Diphenhydramine, 50 mg oral	Memory
	20						
	19	Atopic/active			22	Acrivastine+P, 60 mg oral	
	20	Atopic/active			22	Placebo	
		Normal			28	Normal/control	
		Atopic/active			24	Diphenhydramine, 50 mg oral	
		Atopic/active			22	Acrivastine+P, 60 mg oral	
		Atopic/active			22	Placebo	
		Normal			28	Normal/control	
		Atopic/active			24	Diphenhydramine, 50 mg oral	
		Atopic/active			22	Acrivastine+P, 60 mg oral	
		Atopic/active			22	Placebo	
		Normal			28	Normal/control	
Vuurman et al, 1993[22]	11	Sar	Industry	Parallel groups	18	Diphenhydramine, 25 mg oral	Memory
					17	Loratadine, 10 mg oral	
					17	Placebo	
Weiler et al, 2000[23]	31	Sar/histor	Industry	Crossover	40	Diphenhydramine, 50 mg oral	Self-report
					40	Fexofenadine, 60 mg oral	
					40	Placebo	
Witek et al, 1995[24]	23	Normal	Industry	Crossover	18	Diphenhydramine, 50 mg oral	Self-report, attention
					18	Terfenadine, 60 mg oral	
					18	Placebo	
Witek et al, 1995[24]	29	Normal	Industry	Crossover	20	Diphenhydramine, 25 mg oral	Self-report, attention
					20	Diphenhydramine, 50 mg oral	
					20	Chlorpheniramine, 4 mg oral	
					20	Placebo	

bid, Twice daily; *qd,* every day; *iv,* intravenous; *sar,* seasonal allergic rhinitis; *histor,* historical.

Diphenhydramine versus second-generation antihistamines

Diphenhydramine also decreased performance scores in comparison with second-generation antihistamines. Mean ESs were calculated for performance comparisons between groups treated with diphenhydramine and one of the second-generation antihistamines, including acrivastine, astemizole, cetirizine, fexofenadine, loratadine, or terfenadine (Fig 1, *B*). Across measures and studies, the average ES of 0.31 was significant (95% CI, 0.17-0.45; $P = .0001$) and again indicative of a moderate diphenhydramine performance impairment. As with the diphenhydramine versus placebo comparison, marked variability was observed, and not all studies reported diphenhydramine-induced sedation. Significant mean ESs emerged on 3 of the 6 individual measures, including self-report (ES = 0.45; 95% CI, 0.01-0.26; $P = .045$), attention (ES = 0.35; 95% CI, 0.05-0.64; $P = .029$), and evoked brain potential (ES = 0.53; 95% CI, 0.17-0.89; $P = .018$). The ES of 0.21 for memory approached significance (95% CI, 0.03-0.42; $P = .050$). Although few studies included reaction time or evoked brain potential measures, results from these appeared consistent with the overall ES finding (Fig 1, *B*).

Second-generation antihistamines versus placebo

Placebo results were contrasted with those of the second-generation antihistamines, including acrivastine, astemizole, cetirizine, fexofenadine, loratadine, or terfenadine (Fig 1, *C*). When all 6 performance measures were averaged, a small but significant ES resulted (ES = 0.14; 95% CI, 0.01-0.26; $P = .030$), indicating sedation in the groups treated with second-generation antihistamines relative to placebo. The second-generation antihistamines responsible for positive ESs, indicating self-reported sedation or impaired performance, were varied and included acrivastine, astemizole, cetirizine, loratadine, and terfenadine. On the individual measures, the ES was significant only for self-report (ES = 0.39; 95% CI, 0.05-0.74; $P = .030$), although the ES approached significance for reaction time (ES = 0.22; 95% CI, –0.06 to 0.49; $P = .10$). Although fewer than 5 studies were available for measures of attention, dexterity, or evoked brain potential measures, the results appeared consistent with an overall small sedation effect.

Additional factors potentially influencing outcomes

Other potential mediating variables, including source of funding, medication dose, days of treatment, presence or severity of allergic symptoms, and subject age, race, and sex were coded but could not be analyzed because they were infrequently reported or, in the case of medication dose, because there was little variation across studies (eg, diphenhydramine was most commonly administered at 50 mg, cetirizine at 10 mg, and loratadine at 10 mg).

DISCUSSION

Diphenhydramine can cause sedation. On most measures included in this meta-analysis, diphenhydramine produced evidence of sedation in comparison with placebo or second-generation antihistamines. The overall ES of 0.36 represents a moderate sedation factor. In some studies the ES was dramatically large. However, the size and direction of results varied markedly. In some cases differences indicated less sedation in the diphenhydramine group than in the comparison group. Differences across studies in size, direction, and variance of specific measures were not explained by differences in study drug, design, or subject characteristics.

In this meta-analysis, limited to performance-impairment studies that included diphenhydramine, no second-generation antihistamine produced performances consistently superior to those of the placebo and diphenhydramine conditions, including the 2 drugs no longer marketed in the United States, terfenadine and astemizole. Second-generation antihistamines were not nonsedating, although sedation effects were weaker than for diphenhydramine. The overall ES of 0.14, indicating sedation effects in second-generation antihistamines versus placebo, was small but significant. The ES of 0.39 for self-report measures was as large as that seen when diphenhydramine was compared with placebo. The absence of a consistent diphenhydramine sedation effect was unexpected given that most studies were designed to enhance the probability of observing diphenhydramine sedation. For example, in 15 of the 18 studies, subjects were provided 50 mg of diphenhydramine, the maximum standard dose. Outcome measures reported and included in this meta-analysis were taken at peak serum concentrations 2 to 4 hours after dosing. Additionally, dosing and evaluation in most cases were conducted on the initial day of medication use before the tachyphylaxis to the sedation effect could occur.

That few studies are available to evaluate the effect of 25 mg of diphenhydramine is remarkable given that diphenhydramine is most commonly sold in 25-mg tablets, and an undetermined number of adults take a 25-mg dose. Individual studies that included diphenhydramine at 25 mg reveal inconsistent results, with some detecting impaired performance[21,24] and others not.[7,16] If consumers are to make an informed judgment about relative risk and benefits, then the histamine-suppressing capacity and sedation effects of 25 mg of diphenhydramine must be concurrently compared with those of second-generation antihistamines within a single study. Equipotency, a basic principle followed in comparative studies of adverse consequences of medications, calls for the use of clinically equivalent doses of drugs under investigation. Given recent new evidence that untreated allergic rhinitis can impose significant impairment on cognitive vigilance, speed, and efficiency,[27] it will be of additional interest to assess performance differences between antihistamines and within differing doses of the same antihistamine relative to performance impairment

caused by the illness itself. Further benefits of antihistamine studies will be realized if they include detailed information about the subjects studied, including an accounting of whether any subjects dropped out of the study because they experienced sedation. Despite their widespread use with children, very few studies have examined sedation and performance impairment in children using first- or second-generation antihistamines. Two studies have measured the consequence of administering 25 mg of diphenhydramine, the maximum recommended dose, to children. One found that computer-measured learning scores of children treated with diphenhydramine were lower than those of children treated with loratadine,[22] whereas a second study that followed children treated with the same 2 drugs through four 8-hour days in a laboratory school found no differences in learning, reaction time, or self-ratings of sedations.[7] There exists an inadequate number of pediatric studies to establish a superiority of second-generation antihistamines in children with rhinitis sufficient to justify their large expense over diphenhydramine. The need clearly persists for further research with children.

Results from this meta-analysis provide guidance for the choice of measures for future sedation studies. Self-report, reaction time, attention, and P300 measures produced the largest overall ESs, suggesting that these are the most sensitive measures. However, very few reaction time and P300 studies were represented in the analyses, and hence the choice of these measures warrants less confidence at the present time than the use of self-report and attention. Evoked potential measures provide physiologic evidence of a drug effect, but little is known about whether the small changes detected in these studies, typically presented as the percentage change from baseline, correspond to a meaningful change in human performance. Whatever the measure used, investigators must clearly state the measure of variance they are reporting (eg, SD vs SE) to allow the comparison of ES across studies.

Although data are not plentiful, studies weigh toward more performance disruption and sedation with diphenhydramine than placebo or so-called nonsedating antihistamines. Given the importance of providing optimal care, as well as maximizing safety, one can see why nonsedating antihistamines are widely prescribed. Yet the information that we have is far from definitive, and the sedating effects of allergic rhinitis have not been consistently separated from the sedating effects of the drugs used to treat it. Diphenhydramine continues to be the most extensively used over-the-counter medication for the treatment of allergic rhinitis; an estimated 47% of persons with allergies take over-the-counter products, most containing a first-generation antihistamine.[23] True experimental studies that control for effects of dose, dosing regimen, and dose timing are needed to resolve this dilemma.

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