Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis
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CRD summary
This poorly reported review compared the sedating and performance-impairing effects of diphenhydramine versus placebo and second-generation antihistamines. The authors' concluded that no clear and consistent differences existed between diphenhydramine and second-generation antihistamines. Although the review has a number of methodological limitations, the authors' are right to call for further research to clarify the mixed results of the included studies.

Authors' objectives
To compare the effect of diphenhydramine with placebo and second-generation antihistamines on sedation and performance.

Searching
MEDLINE was searched from 1966 to January 2002 for studies published in English in peer-reviewed journals; the search terms were stated. The reference lists in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
Blinded, randomised controlled trials (RCTs) with a placebo control were eligible for inclusion. The studies had to report the mean and variance (standard deviation or standard error). The included studies were of a crossover or parallel-group design.

Specific interventions included in the review
Studies of diphenhydramine were eligible for inclusion. Most of the included studies used 50 mg diphenhydramine but a few used 25 mg. The included studies compared diphenhydramine with placebo or with second-generation antihistamines (e.g. acrivastine, astemizole, cetirizine, fexofenadine, loratadine and terfenadine), or compared second-generation antihistamines with placebo.

Participants included in the review
Studies of atopic patients, whether symptomatic or not, were eligible for inclusion. The participants were aged from 8 to 81 years.

Outcomes assessed in the review
Studies that assessed self-reported sleepiness, attention, memory, reaction time, eye-hand coordination, or evoked brain potentials, were eligible for inclusion if the outcomes were measured in the laboratory. Most of the included studies assessed the outcomes on the first day of drug use.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted and coded the data, and resolved any disagreements through discussion. For each outcome, the standardised effect size (ES) of the difference between treatment groups was calculated for each study.

Methods of synthesis

How were the studies combined?
The studies were combined in meta-analysis using a random-effects model. The pooled ESs and 95% confidence intervals (CIs) were estimated, with individual ESs weighted by the inverse of the variance. The average ES across all six outcome measures was calculated, in addition to an ES for each outcome measure. Pooled ES were calculated for diphenhydramine versus placebo, diphenhydramine versus any second-generation antihistamine, and second-generation antihistamines versus placebo.

How were differences between studies investigated?
The variability of the results across the studies was commented upon, but no formal tests of statistical heterogeneity were performed. The authors stated that it was not possible to assess the influence of potential confounding factors (such as demographic or clinical variables, drug dose and duration of treatment) due to the lack of appropriate data.

Results of the review

Eighteen RCTs (1,444 patients) were included.

Diphenhydramine versus placebo.

Diphenhydramine was significantly more sedative than placebo over all outcome measures, but the results varied among the studies; the average ES was 0.36 (95% CI: 0.20, 0.51, P=0.0001). Not all studies showed more sedation with diphenhydramine. The ES for diphenhydramine versus placebo was significant for impaired attention (at least 8 RCTs, ES 0.53, 95% CI: 0.36, 0.71, P=0.0001). There was no significant difference between diphenhydramine and placebo for reaction time (3 RCTs), dexterity (4 RCTs), or evoked brain potential (2 RCTs). Diphenhydramine increased self-reported sedation (at least 11 RCTs, ES 0.41, 95% CI: -0.07, 0.90, P=0.089) and memory (at least 8 RCTs, 95% CI: -0.01, 0.33, P=0.051), but the difference in impairment was not statistically significant.

Diphenhydramine versus any second-generation antihistamine.

Diphenhydramine was significantly more sedative than second-generation antihistamines over all outcome measures, but the results varied among the studies; the average ES was 0.31 (95% CI: 0.17, 0.45, P=0.0001). Not all studies showed more sedation with diphenhydramine. Diphenhydramine significantly increased self-reported sedation, impaired attention and impaired evoked brain potential compared with second-generation antihistamines; the ES was 0.45 (95% CI: 0.01, 0.26, P=0.045) for self-reported sedation (at least 11 RCTs), 0.35 (95% CI: 0.05, 0.64, P=0.029) for attention (6 RCTs), and 0.53 (95% CI: 0.17, 0.89, P=0.18) for evoked brain potential (3 RCTs). It should be noted that the ES for self-reported sedation (0.45) appears to be in error since it lies outside the reported confidence range (95% CI: 0.01, 0.26). Diphenhydramine also increased memory impairment but this increase was not statistically significant; the ES (5 RCTs) was 0.21 (95% CI: 0.03, 0.42, P=0.050).

Second-generation antihistamines versus placebo.

Second-generation antihistamines were significantly more sedative than placebo over all outcome measures, but the difference was small and the results varied among the studies; the average ES was 0.14 (95% CI: 0.01, 0.26, P=0.030). Self-reported sedation was the only individual measure on which second-generation antihistamines showed significant impairment compared with placebo; the ES (at least 9 RCTs) was 0.39 (95% CI: 0.05, 0.74, P=0.030). Second-generation antihistamines also increased reaction time compared with placebo but this increase was not statistically significant; the ES (4 RCTs) was 0.22 (95% CI: -0.06, 0.49, P=0.10).

Authors’ conclusions

The results on the sedating effects of diphenhydramine differed among the studies. The studies showed no clear and
consistent differences between diphenhydramine and second-generation antihistamines.

CRD commentary
The review question was clear in terms of the study design, intervention and outcomes. The review’s inclusion criteria restricted participants to atopic patients, but some of the included studies also had normal patients and it was not stated whether or not these patients were excluded from the analysis in the review. Limiting the included studies to English language publications listed in one database may have resulted in the omission of other relevant studies. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. The methods used to select the studies were not described; hence, any efforts made to reduce errors and bias cannot be judged. Two reviewers independently extracted the data, thus reducing the potential for bias and errors. Only blinded RCTs were eligible, but validity was not formally assessed and the quality of the evidence presented could not be judged.

Some relevant information on the individual studies was tabulated. A meta-analysis was performed, without an assessment of statistical or clinical heterogeneity. The authors stated that the lack of appropriate data precluded the exploration of mediating factors. The evidence appears to have been based largely on assessments conducted on the first day of drug treatment; longer term sedative effects may differ. The review showed that the results on the sedating effect of diphenhydramine appeared to differ among the studies, but this was not explored. An assessment of the influence of study validity on the results might have helped clarify conflicting results. It was unclear whether the studies used an appropriate comparator dose. The review also assessed second-generation antihistamines versus placebo, but only studies that also had a diphenhydramine treatment arm were included. Thus, some relevant studies may have been omitted. The ES in the review should be interpreted in the light of the methodological limitations highlighted. However, the authors’ comments on the need for further research, to clarify the mixed results on the sedative effect of diphenhydramine, appear justified.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that research is required to assess the relative efficacy of different doses, regimens and timing of the same antihistamine in relation to performance impairment, and to compare diphenhydramine with second-generation antihistamines in children with rhinitis. They also stated that future reports of antihistamine research should include information on participants and drop-outs due to sedation, and clearly state which measure of variance was used.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.