

Antihistamine meta-analysis leaves uncertainty

Key words: *Nonsedating antihistamines, diphenhydramine, sedation, performance impairment, cost/benefit ratio*

One can sense ambivalence and perhaps even angst in the valuable meta-analysis by Bender et al entitled "Sedation and performance impairment of diphenhydramine and second-generation antihistamines: A meta-analysis."¹ Ironically, the authors list several purposes of meta-analysis, including to "resolve uncertainty when studies disagree." Yet the reader cannot help but feel uncertain and perhaps uncomfortable about the hesitation to endorse therapy that produced fewer side effects in the face of the documented moderate sedative and performance-restricting effects of diphenhydramine compared with those of placebo and the less robust but significant sedative effects of this first-generation antihistamine compared with those of second- and third-generation agents. How significant do significant results of a meta-analysis have to be to be accepted as significant? How often do all the studies that meet entry criteria show exactly the same results? If they do show uniformity, why bother with a meta-analysis?

The authors declare that the information is not definitive in favor of the less-sedating and performance-restricting options and that the results of all studies are not consistent. Although they aim to "provide physicians and consumers with a clearer understanding of the relative risks associated with (diphenhydramine) use," the authors are stuck with lackluster yet significant findings of less sedation and performance impairment by so-called nonsedating antihistamines and cannot move to a conclusion that these more expensive agents should be rejected in favor of the less expensive but more sedating alternative.

Attempting to balance a number of variables, the authors conclude that studies weigh toward more performance disruption and sedation with diphenhydramine than with newer agents. They recognize the importance of the so-called nonsedating antihistamines for "providing optimal care, as well as maximizing safety."¹ Nevertheless, they are concerned about the quality of the trials that fit their criteria, the particular deficiencies in the number and quality of pediatric trials, and the quandary of the risk/benefit ratio and financial consequences to our society.

There is good reason for concern about these trials. Only 18 studies survived the weeding-out process, which restricted entries to articles written in English that were blinded randomized trials with a placebo arm, were focused on atopic disease, contained laboratory measures of sedation or psychomotor performance, and included a measure of variance. The sample size per study varied from 6 to 40. The majority of trials that were included were industry supported, with only 2 being purely government supported (ie, a crossover trial of 20 patients and another of 6 patients). Six studies fail to report a funding source. This certainly reflects a major discrepancy in the level of pharmaceutical funding for trials aimed at proving safety and efficacy to gain Food and Drug Administration approval, which demands hundreds of subjects, versus those to clarify more subtle but equally important variables, such as psychomotor effects.

The weaknesses in pediatric data on the nonsedating antihistamines are particularly glaring. The Bender article states that there are inadequate studies in children to establish superiority of these drugs sufficient to justify their expense. For adults and children, the authors express concern that the self-report, reaction time, attention, and P300 measures, which demonstrated the largest effects in support of relatively nonsedating antihistamines, were not examined in a uniform way among the included studies. Again, we see a conflict between the statistically valid conclusion that so-called nonsedating antihistamines provide less effect on psychomotor function than diphenhydramine and a less-than-enthusiastic endorsement of these products.

Is this not a moral dilemma for the clinician? We see that the nonsedating antihistamines are not so very different from older versions, and we know they are expensive. Then again, the meta-analysis was positive for their being less sedating and performance impairing than the older antihistamines. Who should bear the emotional and financial risk of choosing diphenhydramine over the newer products? Who is willing to put the global figure of cost of these agents above the vow to do no harm to the individual patient? Which of us wants to opt for the therapy that might cause psychomotor retardation that we cannot consciously appreciate but that is real for ourselves, our own children, or our patients?

Third-party payers are inclined to remove the decision making from the physician and the patient by limiting approved formularies and levying hefty copays on popular products in an effort to control costs. In creating these onerous obstacles, there is no clear statement from these impersonal businesses regarding optimal care for the individual or burden or risk, only the cost/benefit ratio to society or, should we say, to their balance sheets? Although we can point a finger at direct-to-consumer

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Received for publication January 16, 2003; revised January 23, 2003; accepted for publication January 23, 2002.

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J Allergy Clin Immunol 2003;111:695-6.

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0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.1410

advertising and frivolous propaganda that inflates the cost of health care, let us not forget that the Bender meta-analysis showed moderate sedation caused by diphenhydramine compared with that caused by placebo and less performance disruption and sedation than the so-called nonsedating antihistamines.

What will happen now that these products are entering the over-the-counter world? What will be the socioeconomic implications of these changes? A recent "micro-analysis"² of the effect of the switch of second-generation antihistamines from prescription to over-the-counter status concluded that it is uncertain that this would be cost saving to society, depending on pricing strategies and consumer behavior, which are still unknowns. It appears that, at least for a while, both branded and generic versions will be considerably more expensive than drugs obtained by means of prescription with copays of the past. Will there be more untreated disease, more drowsiness, and more lawsuits regarding injuries and accidents that might be related to failure to recommend a less-sedating alternative to inexpensive therapy? How can the cost of these possibilities be factored into decision making regarding access to less-sedating medications? What will be the ethical fallout of this attempt at cost containment?

These queries ask about the future. Can we answer them by looking back to life before terfenadine? Certainly, health maintenance organizations that attempted to restrict availability of this product years ago were thwarted by threats and realities of litigation related to sedation and performance and succumbed to this pressure. The William M. Mercer employee benefits consultant company used an actuarial model that revealed a \$2 to \$4 gain in productivity for every \$1 spent when patients with allergies used nonsedating instead of sedating treatments.³

One likely approach to cost increases is a switch to therapeutic alternatives. This could decrease the cost of care if patients tend to use monotherapy with topical nasal corticosteroids or topical antihistamines rather than combination therapy with both oral antihistamines and topical sprays. Alternatively, montelukast could be substituted for

antihistamine tablets, returning cost levels to where they have been with prescription antihistamines combined with nose sprays. A comeback position by insurance companies could be an increase in the level of the montelukast copay, which would be a barrier to asthma care.

The age-old practice of immunotherapy might have another renaissance, despite years of unsuccessful attempts to gain approval for immunogenic options with less risk of adverse effects than agents that are currently available. Is there a chance that monoclonal antibody therapy will become cost effective for patients with rhinitis?

And then there is the fearful question that weighs on some practitioners: Will patients drop us if they can get nonsedating antihistamines on their own? I venture to guess that most allergy specialists see only a smattering of patients with uncomplicated rhinitis who use antihistamine monotherapy. Some formal evaluation of this statement and an analysis of changes in practice patterns over the next few years will be important to our specialty as we assess our present-day situation and our manpower needs in the future.

If these unanswered questions leave one unsettled, imagine how Dr Bender and his colleagues felt in writing their meta-analysis. They surely worried about the quality of the data and also about the socioeconomic ramifications of their conclusions. Many of us are worried about all of this.

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