
Performance impairment revisited

Symptoms resulting from nasal allergy are caused by the intensity of the inciting agent, the host response, and a subjective element of perception. This may explain why clinical studies are often negative when intuition (and clinical pharmacology) would predict a positive outcome. When developing new drugs for allergy, several additional studies are often required to be conducted by pharmaceutical companies to obtain the two positive well controlled studies needed to obtain approval for marketing.

Attempts have been made to control environmental conditions under which allergy is studied to better understand the effect size of an intervention. Examples of these include nasal provocation challenge techniques, environmental challenge chambers, and rigorously controlling inclusion and exclusion criteria for controlled clinical trials. These attempts are often limited in scope, and are logistically challenging given the need to study large numbers of clinical trials subjects administered drugs with modest efficacy and a large placebo effect.

Despite efforts to standardize methodology and present guidelines for drug evaluation, there are a wide variety of clinical models in use and many unanswered questions. For example, there is still some controversy as to whether seasonal and perennial allergic rhinitis is the same disease entity with a longer duration. The effect of symptomatic disease on clinical trial measures including performance has not been studied extensively.

When considering quality of life, performance impairment is a critical variable to consider. Performance impairment has not been well defined. We may have an intuitive feel for what we understand by the term, but there is no consensus on a definition, nor on methods to test effects on it. Further, the tests applied under controlled conditions have not been demonstrated to correlate with epidemiologic studies that may more accurately reflect real-life experience. Terms that are used commonly in the allergy literature such as sedation, fatigue and asthenia are also poorly understood. Various methods have been proposed to evaluate performance impairment and have been published. Although there are several well recognized paradigms to evaluate efficacy and safety of drugs in allergic rhinitis clinical trials, the methods that primarily address performance impairment are less standardized and the validity of some has been debated.^{1,2}

In this edition of the *Annals*, Wilken and Kane³ have developed techniques to control the environment while measuring performance impairment. A battery of automated neuropsychologic tests was administered to asymptomatic adult subjects with histories of allergic rhinitis. The subjects were divided into two groups. One group was exposed to ragweed

pollen in a controlled exposure setting until they demonstrated predetermined severities of allergic rhinitis symptoms. The other group was not exposed to pollen in the environmental unit and had minimal symptoms. The battery of cognitive tests was re-administered to both groups. The interesting observation was that allergic rhinitis had major adverse impacts on measures of vigilance. This trial is supported by Spaeth et al⁴ who conducted several clinical trials with oral antihistamines (including mizolastine, cetirizine, loratadine and astemizole) and topical azelastine nasal spray. They concluded that any truly threatening sedation results from the disorder itself. However, these are in contrast to a previous study that demonstrated small effects.⁵

Laboratory studies do allow for greater control of dependent variables, especially the level of allergen exposure. Indeed, it has been traditional to record pollen counts during a clinical efficacy study so that there can be some assurance that symptomatic subjects were exposed to the pollen to which they are known to be sensitive. However, with the large size of typical trials it is unrealistic to run an entire cohort of subjects through the study at exactly the same time. Further, subjects spend most of their working days indoors, and outdoor pollen exposure is even more variable. Data from "day in the park" studies and exposure in the environmental exposure chamber can currently be used to supplement traditional efficacy data, but are not admissible as substitutes for traditional trials.

It is tempting to speculate that the disease itself may in fact cause certain adverse effects that have been ascribed to drugs. However, before we call for wholesale reconsideration of previous data, it is important to stress that the link between laboratory-related studies and real life has not been demonstrated. Although the standardized disease burden may affect the laboratory tests as described in this paper, the effect in real life is not yet demonstrated. The inferences that the authors discuss are speculative, in the absence of data. The degree to which individuals compensate or increase vigilance has not often been measured. In a similar way, studies on driving performance obtained in the laboratory have not been shown to correlate with epidemiologic data on motor vehicle accidents. However, the data from this trial do bring in to question the effects of the primary disease on outcome variables especially related to performance and sedation.

Performance impairment studies often reach simple conclusions but are difficult to interpret. By way of example, Tagawa et al⁶ studied the effects of ebastine and (+)-chlorpheniramine on cognitive tasks. Normal, healthy male subjects between the age of 21 and 24 were studied at times when

plasma drug concentrations were expected to be at their maximum. Based on statistical difference between the study groups, the authors concluded that ebastine 10 mg, as compared with chlorpheniramine 2 and 6 mg did not cause cognitive impairment. However, there is no mention of whether the statistical difference was clinically significant and no correlation between the test results and what might be expected in a real-life task situation.

Recent work, presented at the last Annual Meeting of the American Academy of Allergy, Asthma and Immunology, presents interesting data demonstrating that symptomatic allergic rhinitis increases sleep fragmentation, which would lead to daytime performance impairment.⁷

There have been other recent initiatives to introduce more rigor into rhinitis trials. At the annual meeting of the American Academy, two abstracts were presented highlighting the limitation of clinical trial techniques. One abstract was presented that discussed the importance of treatment effect size. Conducting studies with large populations merely to obtain statistical superiority over placebo is not acceptable to justify an efficacy claim. Type II error is often ignored, and power analyses are often not presented in the statistical section of publications.^{8,9}

Further studies are emerging that evaluate the association between rhinitis and common mental disorders. Goodwin¹⁰ recently reported that there is a relationship between self-reported hay fever and increased likelihood of panic attacks in the general population. As Goodwin¹⁰ notes, prospective, longitudinal epidemiologic data may be useful to improve our understanding of this observed link. In an accompanying editorial, Tilles¹¹ stressed the necessity for allergists to understand the relationship between allergic rhinitis and its potentially related co-morbidities. Further work in this area will go far to enhance our understanding not only of the disease but also on the true effect of interventions.

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