



STANFORD UNIVERSITY SCHOOL OF MEDICINE

VA PALO ALTO HEALTH CARE SYSTEM

Medical Service (111)

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Ms Wanda K. Jones
Deputy Assistant Secretary for Health
Office of Women's Health
Department of Health and Human Services
330 Independence Avenue, SW
Washington, DC 20201

Dear Ms Jones,

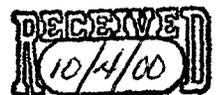
It has recently been brought to my attention that a meeting originally designed to cover safety issues associated with products containing ephedra alkaloids also addressed the findings of a recent study of the safety of phenylpropanolamine-containing drug products. I would like to express some of my concerns about this. Much of my career as a pharmacologist has been devoted to research involving the actions of sympathomimetic amines, a large family of compounds that includes ephedra and phenylpropanolamine. In addition I have written textbook chapters in several standard pharmacology books covering this class of drug. I enclose my CV so that you can have a better idea about my background.

I am concerned for a number of reasons by the joining of these drugs, especially they are not dealt with on their own separate merits:

1. Structure activity relationships. The exact structure of these drugs is critical in determining their pharmacological actions. Even the various stereoisomers of ephedra alkaloids are not the same in their various actions, let alone equivalent to the effects of PPA.
2. Ephedra alkaloids containing multiple isomers, and PPA would generally be expected to have different fundamental pharmacology in terms of activation of adrenergic receptors, either directly or indirectly. In addition, the potency and pharmacokinetics of these drugs are not the same.
3. These differences would be expected to translate into different effects on human target tissues so that it should not be assumed their favorable or adverse effects would be the same.
4. A major difficulty for ephedra alkaloids in herbal preparations is uncertainty in purity, composition of the various isomers, and dose in any given lot. This variability is not an issue for chemically defined preparations of PPA (or ephedrine available from pharmaceutical sources).
5. Based on the published scientific literature, it is my opinion that the effects of PPA on blood pressure in recommended doses are generally small and well within the variation in blood pressure that typically occurs in normal people during the course of the day.
6. The effects of sympathomimetic drugs on the cardiovascular system, especially on the heart versus arteries, are frequently different when members of this class of drug are compared.
7. At recommended doses, I am not aware of any evidence demonstrating that PPA promotes drug seeking behaviors.

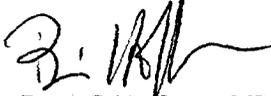
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In conclusion, I would like to emphasize that sympathomimetic drugs typically have different pharmacological effects. In assessing their potential actions in humans, it is important to take into account these pharmacological differences; heavy reliance should be placed on the outcomes of definitive clinical studies aimed at determining the efficacy and safety of each of these drugs. The problem for interpreting data involving crude ephedra alkaloids derived from herbal preparations is complicated by variations in many factors, including uncertainties about dose and detailed drug composition of various preparations. I would encourage you to not paint all sympathomimetic's with the same brush.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'B. Hoffman', with a long horizontal flourish extending to the right.

Brian B Hoffman, MD
Professor of Medicine and Molecular Pharmacology