

Stephan Weidinger, MD^{a,c}
Natalija Novak, MD, PhD^d
Norman Klopp, PhD^e
Hansjörg Baurecht, PhD^b
Stefan Wagenpfeil, PhD^b
Lars Rummeler, MD^a
Johannes Ring, MD, PhD^{a,c}
Heidrun Behrendt, MD^c
Thomas Illig, PhD^e

From ^athe Department of Dermatology and Allergy Biederstein and ^bthe Institute for Medical Statistics and Epidemiology, Technical University Munich; ^cthe Division of Environmental Dermatology and Allergy, GSF National Research Center for Environment and Health/Technical University Munich; ^dthe Department of Dermatology and Allergy, University of Bonn; and ^ethe Department of Epidemiology, GSF-National Research Center for Environment and Health, Neuherberg, Germany.

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Oral phenylephrine: An ineffective replacement for pseudoephedrine?

To the Editor:

In 1976, a US Food and Drug Administration (FDA) review panel concluded that oral phenylpropanolamine, pseudoephedrine, and phenylephrine are safe and

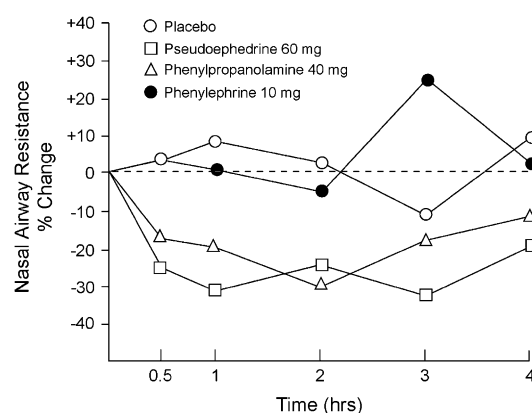


FIG 1. Percent change in nasal airway resistance in 20 patients with chronic nasal stuffiness after single doses of placebo and 3 oral decongestants administered in a randomized, double-blind, crossover manner on different days. Changes were significant at each time point after pseudoephedrine and phenylpropanolamine but not after phenylephrine. Drawn from data presented by Bickerman.⁵ This graph was previously published¹¹ and is reproduced with permission of *Pharmacotherapy*.

effective for nonprescription relief of nasal congestion caused by the common cold, allergic rhinitis, and sinusitis.¹ They are α -adrenergic agonists that decrease nasal mucosal swelling by vasoconstriction.

In 2000, phenylpropanolamine was voluntarily removed from all products because hemorrhagic strokes were associated with its use.² Recently, 34 states have enacted restrictions on the availability of pseudoephedrine because it is used to manufacture methamphetamine illegally. Some states require products containing this decongestant to be sold by a pharmacist or "behind the counter," whereas others restrict the quantity sold. Effective September 30, 2006, an amendment to the USA Patriot Act (HR 3889, Title VII) will require all stores to keep pseudoephedrine products behind the counter and purchasers will have to show a photo identification and sign a log book to obtain them.

Although these actions are unlikely to prevent patients from obtaining pseudoephedrine-containing products from pharmacists, it is increasingly difficult to obtain them from grocery, discount, and convenience stores. In response, Pfizer, Inc (Morris Plains, NJ), introduced a replacement product containing 10 mg phenylephrine (Sudafed-PE) that cannot be converted to methamphetamine and can be sold without restriction. Other manufacturers are following suit.

Phenylephrine, at the FDA-approved dose of 10 mg for adults, is unlikely to provide relief of nasal congestion. It has poor oral bioavailability because of extensive first-pass metabolism in the gut and liver.³ Only 38% of the dose reaches the systemic circulation,³ compared with 90% of a pseudoephedrine dose.⁴ Moreover, in a randomized, double blind, placebo-controlled, crossover study of 3 oral decongestants in 20 patients with chronic nasal stuffiness, phenylephrine was no more effective than placebo in reducing nasal airway resistance⁵ (Fig 1).

(Reference 5 is available in the Online Repository at www.jacionline.org.)

Two published reports indicate a correlation between decrease in objective measurement of nasal airway resistance and improvement in subjective symptom scores after oral decongestants.^{6,7} McLaurin et al⁶ compared single doses of 4 oral decongestants with placebo in a randomized, double-blind, crossover study in 88 patients with nasal congestion from a variety of causes. They concluded that 10 mg phenylephrine was no more effective than placebo in decreasing either nasal airway resistance or subjective symptom scores. In contrast, ephedrine 25 mg was effective for both endpoints, and objective improvement correlated with subjective relief.

In the second report,⁷ 3 different panels of 16 patients with nasal stuffiness from a common cold were studied. Each panel took placebo and either 10 mg, 15 mg, or 25 mg phenylephrine in a randomized, double-blind, crossover manner on 2 consecutive mornings. Symptom scores were significantly reduced for all 3 doses compared with placebo, but there was no difference between doses. In contrast, there was a dose-response relationship for decrease in nasal airway resistance. It is noteworthy that in the cohort treated with 10 mg, baseline nasal airway resistance was significantly different on the 2 study days, making the results difficult to interpret.

As proof of efficacy, the FDA panel cited unpublished, manufacturer-sponsored studies conducted by commercial testing laboratories.¹ One study involved 2 immediate-release 5-mg tablets (Whitehall Laboratories, Inc, New York, NY). The remainder were studies of various doses (up to 25 mg phenylephrine) of immediate-release Neosynephrine tablets (Sterling-Winthrop, New York, NY). All of these studies evaluated both objective and subjective endpoints. Also, they cited studies conducted by other testing laboratories, as well as the 2 we have commented on,^{5,6} that did not demonstrate a significant difference from placebo for either symptom relief and/or nasal airway resistance. In total, for the 10-mg dose, the panel cited only 4 studies demonstrating efficacy compared with 7 demonstrating no difference between this dose and placebo. Thus, in our view, the panel reached a specious conclusion that was not based on a systematic review of the available data.

It is possible that poor bioavailability can be overcome by increasing the dose of phenylephrine, but adequately powered dose-response studies are required to determine whether this will increase efficacy safely. In the meantime, healthcare providers can recommend that patients obtain pseudoephedrine from a pharmacist if they require an oral decongestant for sinusitis or eustachian tube dysfunction. For patients with nasal stuffiness from a common cold, they can recommend a topical nasal decongestant, which is more effective than oral decongestants.⁸ However, a topical decongestant should be avoided by patients with allergic rhinitis because of the risk of rhinitis medicamentosa.⁹ For these patients, an intranasal corticosteroid is likely to provide the greatest relief¹⁰ with low risk of systemic effects.

Leslie Hendeles, PharmD
Randy C. Hatton, PharmD

From the Department of Pharmacy Practice, College of Pharmacy, University of Florida, and the Drug Information Center, Shands Hospital at the University of Florida, Gainesville, Fla.

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Normal lung function in children with mild to moderate persistent asthma well controlled by inhaled corticosteroids

To the Editor:

International guidelines on the diagnosis and management of childhood asthma emphasize the importance of assessing its severity with objective measures of lung function.¹ More specifically, FEV₁ and its reversibility after a bronchodilator are proposed as measures for the severity of childhood asthma, both at initial assessment and during follow-up.¹ Inclusion criteria for many clinical trials in asthma usually include a certain reduction of FEV₁% predicted, along with an improvement of >12% in FEV₁ after bronchodilator.^{2,3} Several studies have shown that FEV₁ levels may improve considerably during treatment with inhaled corticosteroids (ICSs),⁴ and that normal levels of lung function may be attained during ICS treatment.⁵⁻⁷ We tested the hypothesis that children with mild to moderate persistent asthma well controlled on ICS therapy have normal FEV₁ levels and little or no bronchodilator response (BDR), unless they are experiencing a symptomatic episode at the moment of lung function testing, or when their adherence to treatment is poor.