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*Institute for Medical Education*

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The  
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**BULLETIN**

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## Is Pseudoephedrine Safe for Patients with Hypertension?

By  
**Gary Freeman, M.D.**  
With  
**Peter Marshall, PharmD.**

**Developed:** April 2006    **Approved:** May 2006    **Expiration Date for CME Credit:** May 31, 2007  
**Estimated Time to Complete:** 30 Minutes    **Target Audience:** Family Practice, Internal Medicine and Other Primary Care Physicians; Nurse Practitioners and Physician Assistants; Pharmacists; Nurses; Other Health Care professionals

### Description

This learning activity examines the effect of pseudoephedrine on blood pressure and the risk of hemorrhagic stroke.

### Objectives

Following this learning activity, the learner will be able to:

- Name five closely-related sympathomimetic amines.
- Summarize the effect of sympathomimetic amines such as ephedra and phenylpropanolamine on blood pressure and the risk of hemorrhagic stroke.
- Compare the effect of immediate-release pseudoephedrine on systolic and diastolic blood pressure.
- Discuss the results of the Hemorrhagic Stroke Study regarding pseudoephedrine-associated hemorrhagic stroke.

### Accreditation

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### Disclosure of Faculty and Sponsor Relationships

Gary Freeman, M.D. and Peter Marshall, PharmD have indicated no financial interests, affiliations, or intent to discuss unapproved or investigative use of commercial products or devices.

### Evaluation

When you have finished studying these materials, please complete the post-test and evaluation and return them to:

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By  
**Gary Freeman, M.D.**  
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### Is Pseudoephedrine Safe for Patients with Hypertension?

*Pseudoephedrine Less Likely than Other Sympathomimetic Amines to Elevate Blood Pressure  
and Increase Risk of Hemorrhagic Stroke*

**P**seudoephedrine is commonly used for relief of nasal congestion associated with viral respiratory infections or allergies. Patients with hypertension are often reluctant to take this medication because of concern that it will adversely affect their blood pressure and increase their risk for cardiovascular/cerebrovascular events such as hemorrhagic stroke. **Recent evidence suggests that pseudoephedrine is less likely than other sympathomimetic amines to elevate blood pressure and increase the risk of hemorrhagic stroke.**

**The sympathomimetic amines include a number of closely related drugs** including pseudoephedrine, ephedrine, ephedra/Ma Huang <sup>(1)</sup>, phenylpropanolamine <sup>(2)</sup>, amphetamine <sup>(3)</sup>, methylphenidate <sup>(3)</sup>, methamphetamine, epinephrine, and norepinephrine. Many of these compounds exert potent stimulant effects on the cardiovascular system and increase the risk of hemorrhagic stroke <sup>(4)</sup> and other cardiovascular/cerebrovascular events due to peripheral vasoconstriction, cardiac stimulation, and blood pressure elevation <sup>(5)</sup>. **Pseudoephedrine, however, is a relatively weak sympathomimetic amine and seems to be less likely to have these effects.**

**A recent meta-analysis concluded that pseudoephedrine produces only small increases in blood pressure and heart rate** and that there is no evidence that these increases are clinically significant. In this study, pseudoephedrine was found to significantly increase systolic blood pressure (0.99 mm Hg) and heart rate (2.83 beats/min), but did not significantly increase diastolic blood pressure (0.63 mm Hg). Patients with hypertension had a slightly greater increase in systolic blood pressure (1.20 mm Hg).

The meta-analysis also found that immediate-release pseudoephedrine preparations elevated systolic blood pressure (1.53 mm Hg), whereas sustained-release preparations had no effect (-0.98 mm Hg). Neither immediate-release nor sustained-release formulations significantly increased diastolic blood pressure. The effect of immediate-release pseudoephedrine on blood pressure was dose related.

The authors of the Hemorrhagic Stroke Project (a case-control study designed primarily to estimate phenylpropanolamine-associated hemorrhagic stroke) also examined the association between pseudoephedrine and the risk of hemorrhagic stroke in their subjects. Among 702 patients with hemorrhagic stroke (subarachnoid or intracerebral hemorrhage), 9 (1.3%) were exposed to pseudoephedrine as a first use (defined as use within 24 hours before stroke and no other use during the preceding two weeks) as compared with 18 of 1376 control subjects (1.3%), yielding an adjusted odds ratio of 1.07 (95% CI 0.45-2.57,  $p = 0.87$ ). Although the odds ratio suggests that the use of pseudoephedrine was not associated with an increased risk of hemorrhagic stroke, a potentially harmful effect could not be excluded at the upper bound of the confidence interval.

## **CONCLUSIONS**

- **Pseudoephedrine generally causes only small increases in systolic blood pressure and heart rate.** Sustained-release pseudoephedrine preparations appear to have less effect on blood pressure than immediate-release preparations and may be safer for patients with hypertension.
- **Pseudoephedrine does not appear to be associated with an increased risk of hemorrhagic stroke.**
- **Most patients with well-controlled hypertension can probably take pseudoephedrine without fear that it will have a clinically significant adverse effect on their blood pressure or increase their risk for hemorrhagic stroke or cardiovascular events.**

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1) Dietary supplements containing ephedra have been banned by the US Food and Drug Administration since April 2004. Ephedra is a plant that contains six ephedrine alkaloids including ephedrine and

pseudoephedrine. Ephedra has been used as a dietary supplement for weight control and increased energy/athletic performance enhancement. An analysis of 43 cases of adverse effects associated with ephedra included 10 deaths and 13 cases of permanent disability. Forty seven percent of these events involved cardiovascular symptoms (hypertension, palpitations, and tachycardia) and 18% involved the central nervous system (stroke and seizures). In addition, the FDA has received more than 16,000 case reports of adverse effects associated with ephedra.

- 2) Based on the results of the Hemorrhagic Stroke Study demonstrating an association between phenylpropanolamine use and hemorrhagic stroke, the Nonprescription Drugs Advisory Committee of the US Food and Drug Administration recommended the voluntary removal of products (over-the-counter weight control and cough/cold preparations) containing phenylpropanolamine from the market in October 2000. In December 2005, the FDA proposed banning the use of phenylpropanolamine from over-the-counter medications.
- 3) In February 2006, the Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration voted to recommend a “black-box” warning describing the cardiovascular risks of stimulant drugs (primarily amphetamines and methylphenidate) used to treat attention-deficit-hyperactivity disorder (ADHD). This recommendation was based on 25 reports from the FDA’s Adverse Event Reporting System of sudden death in children and adults taking one of these medications. Subsequently, the FDA’s Pediatric Advisory Committee recommended that the labeling for these medications include simpler language and more information rather than a “black box” warning.
- 4) The Hemorrhagic Stroke Project, a case-control study of men and women age 18-49 years who had experienced a subarachnoid or intracerebral hemorrhage within 30 days before enrollment, was designed to estimate the association between hemorrhagic stroke and exposure to phenylpropanolamine. The study found that phenylpropanolamine in appetite suppressants was strongly associated with hemorrhagic stroke in women (adjusted odds ratio 16.58; 95% CI 1.51-182.21,  $p = 0.02$ ). Phenylpropanolamine in cough or cold remedies was also associated with an increased risk of hemorrhagic stroke (adjusted odds ratio 3.13; 95% CI 0.86-11.46,  $p = 0.08$ ).
- 5) A meta-analysis of 33 trials with 2165 patients found that phenylpropanolamine increased systolic blood pressure 5.5 mm Hg (95% CI 3.1-8.0 mm Hg) and diastolic blood pressure 4.1 mm Hg (95% CI 2.2-6.0 mm Hg). Immediate release preparations had greater effects on blood pressure than sustained release preparations. Higher doses also caused greater increases in blood pressure. Other studies have demonstrated that mixed amphetamine salts (Adderall) administered to adults increased systolic blood pressure by about 5 mm Hg. Methylphenidate formulations have similar effects on blood pressure. Blood pressure increases of the magnitude caused by phenylpropanolamine and the drugs used to treat attention-deficit-hyperactivity disorder are known to increase cardiovascular morbidity and mortality.

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