

American Academy of Allergy, Asthma & Immunology's and
American College of Allergy, Asthma & Immunology's
Statement of Support of Citizens' Petition for
Removal of Oral Phenylephrine from Over-the-Counter Status
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Nasal congestion is acutely or chronically a bothersome symptom at all ages for the vast majority of people. Oral phenylephrine (PE), phenylpropanolamine (PPO), and pseudoephedrine (PSE) were determined to be safe and effective for nonprescription therapy of nasal congestion by a 1976 Food and Drug Administration panel (FDA).¹ PPO was voluntarily removed from the market in 2000 after it had been associated with hemorrhagic strokes.² Because PSE had been used to illegally manufacture methamphetamine, the Combat Methamphetamine Epi-demic Act of 2005 required all retail stores nationwide to keep products containing PSE "behind the counter."³ Consequently, since PE cannot be converted to methamphetamine and can be sold without restrictions, the manufacturers of oral decongestants have substituted PE for pseudoephedrine in their over-the-counter products. According to a recent article,⁴ PE is now the number one ingredient in oral nasal and sinus products, and it is included in 261 such products. However, there are continuing questions regarding the efficacy for nasal decongestion of PE 10 mg, the maximum FDA-approved dose.

A systematic review and meta-analysis published in 2007⁵ reported that in 8 unpublished studies which included 138 patients with nasal congestion oral PE 10 mg did not affect nasal airway resistance (NAR) more than placebo (PBO). The mean maximal difference in relative change from baseline between PE and PBO was 10.1% (95% CI -3.8% to 23.9%). In 8 unpublished studies of oral PE 25 mg a significant reduction of mean maximal difference of NAR relative to PBO was shown of 27.6% (95% CI 17.5% to 37.7%). NAR was a more sensitive measure of efficacy than subjective reports, with patient reported decongestion not consistently better for any PE dose compared to PBO.

A study of oral PE published in 2015⁶ examined nasal congestion symptom relief of 4 different doses (10, 20, 30, or 40 mg) of PE-HCl immediate release 10 mg tablets or PBO. This multicenter trial randomized 539 adults with seasonal allergic rhinitis. The primary efficacy end point was the mean change in nasal congestion score from baseline over the 7 days of treatment. None of the PE-HCl groups at doses up to 40 mg every 4 hours had a statistically significant change in reflective or instantaneous nasal congestion score compared with the PBO group. Another study⁷ compared a modified release of PE-HCl given as 30 mg every 12 hours for 7 days compared to PBO. This study of 575 patients also showed that PE-HCl in a dose that was higher than the standard FDA approved amount per dose and per day was no different from PBO in the mean change in the nasal congestion score from baseline. There was also no difference between the groups in secondary outcomes such as time to maximal effect, duration of effect or improvement in patient reported quality of life.

Environmental exposure unit studies have also demonstrated no subjective or objective (peak nasal inspiratory flow rate, rhinomanometry) improvements in nasal congestion from PE compared to PBO treatment.^{8,9} Finally, the most recent Joint Task Force Rhinitis Practice Parameter of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology indicate that doses of phenylephrine up to 40mg a day are ineffective.¹⁰

The low bioavailability of pharmacologically active oral PE explains the lack of nasal therapeutic efficacy and cardiovascular effects. It is extensively metabolized in the gut mucosa causing insufficient systemic PE levels to produce vasoconstriction of nasal and other blood vessels.⁴ Available data do not support whether a dose greater than 40mg of oral PE would be effective or safe. Furthermore, the American Academy of Allergy, Asthma & immunology and the American College of Allergy, Asthma & Immunology in their role as patient advocates have concluded that keeping oral phenylephrine over-the-counter does a disservice to patients who might be prone to taking higher doses than recommended due to lack of effect and/or delay their visit to their primary care clinician or a specialist who could help resolve their symptoms.

On the basis of current evidence, the American Academy of Allergy, Asthma & immunology and the American College of Allergy, Asthma & Immunology support the November 4, 2015 Citizen's Petition submitted to the FDA by Drs. Leslie Hendeles and Randy C. Hatton. This petition requests the Commissioner of Food and Drugs remove oral phenylephrine hydrochloride from the Final Monograph for OTC nasal decongestant products and remove phenylephrine bitartrate from the 2006 amendment.¹¹

1. Department of Health, Education, and Welfare. Food and Drug Administration. Establishment of a monograph for over-the-counter (OTC) cold, cough, allergy, bronchodilator, and anti-asthmatic products. Fed Regist 1976;41:38399- 400. <https://www.federalregister.gov/documents/2005/07/13/05-13708/cold-cough-allergy-bronchodilator-and-antiasthmatic-drug-products-for-over-the-counter-human-use>
2. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.
3. Combat Methamphetamine Epidemic Act of 2005 (H.R.3889, Title VII). <https://www.congress.gov/bill/109th-congress/house-bill/3889>
4. Hatton RC, Hendeles L. Why is oral phenylephrine on the market after compelling evidence of its ineffectiveness as a decongestant? Ann Pharmacother. 2022 Mar 25;10600280221081526. doi: 10.1177/10600280221081526. Online ahead of print.
5. Hatton RC, Winterstein AG, McKelvey RP, Shuster J, Hendeles L. Efficacy and safety of oral phenylephrine: systematic review and meta-analysis Ann Pharmacother 2007;41:381-90.
6. Meltzer EO, Ratner PH, McGraw T. Oral phenylephrine for nasal congestion in seasonal allergic rhinitis: a randomized, open label, placebo-controlled study. J Allergy Clin Immunol Pract 2015;3:702-8.

7. Meltzer EO, Ratner PH, McGraw T. Phenylephrine hydrochloride modified-release tablets for nasal congestion: a randomized, placebo-controlled trial in allergic rhinitis patients. *Ann Allergy Asthma Immunol* 2016;116:66-71.
8. Horak F, Ziegelmayer P, Ziegelmayer R, et al. A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna challenge chamber. *Ann Allergy Asthma Immunol* 2009;102:116-20.
9. Day JH, Briscoe MP, Ratz JD, Danzig M, Yao R. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. *Ann Allergy Asthma Immunol* 2009;102:328-338.
10. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, Dinakar C, Ellis AK, Finegold I, Golden DBK, Greenhawt MJ, Hagan JB, Horner CC, Khan DA, Lang DM, Larenas-Linnemann DES, Lieberman JA, Meltzer EO, Oppenheimer JJ, Rank MA, Shaker MS, Shaw JL, Steven GC, Stukus DR, Wang J; Chief Editor(s):, Dykewicz MS, Wallace DV; Joint Task Force on Practice Parameters:, Dinakar C, Ellis AK, Golden DBK, Greenhawt MJ, Horner CC, Khan DA, Lang DM, Lieberman JA, Oppenheimer JJ, Rank MA, Shaker MS, Stukus DR, Wang J; Workgroup Contributors:, Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, Finegold I, Hagan JB, Larenas-Linnemann DES, Meltzer EO, Shaw JL, Steven GC. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. 2020 Oct;146(4):721-767.
11. Citizen's Petition to the US Food and Drug Administration (FDA 2015-P). Dated 11-4-2015 and signed by Leslie Hendeles, PharmD and Randy C. Hatton, PharmD.