Effect of Oral Pseudoephedrine on Blood Pressure and Heart Rate

A Meta-analysis

Stephen M. Salerno, MD, MPH; Jeffrey L. Jackson, MD, MPH; Elizabeth P. Berbano, MD, MPH

Oral pseudoephedrine is commonly used to treat symptoms of rhinitis and rhinorrhea, but its effect on blood pressure (BP) and heart rate (HR) remains uncertain. We assessed whether pseudoephedrine causes clinically meaningful elevations in HR or BP. We searched MEDLINE, EMBASE, and the Cochrane Library for English-language, randomized placebo-controlled trials of oral pseudoephedrine treatment in adults. The primary data extracted were systolic BP (SBP), diastolic BP (DBP), and HR. Study quality was assessed using the methods of Jadad, and data were synthesized using a random-effects model and weighted mean differences. Twenty-four trials had extractable vital sign information (45 treatment arms; 1285 patients). Pseudoephedrine caused a small but significant increase in SBP (0.99, mm Hg; 95% CI, 0.08 to 1.90) and HR (2.83 beats/min; 95% CI, 2.0 to 3.6), with no effect on DBP (0.63 mm Hg, 95% CI, –0.10 to 1.35). The effect in patients with controlled hypertension demonstrated an SBP increase of similar magnitude (1.20 mm Hg; 95% CI, 0.56 to 1.84 mm Hg). Higher doses and immediate-release preparations were associated with greater BP increases. Studies with more women had less effect on BP or HR. Shorter duration of use was associated with greater increases in SBP and DBP.

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Oral pseudoephedrine is a common ingredient in more than 135 over-the-counter and prescription medications.[1,2] Brands of common over-the-counter and prescription decongestants that contain pseudoephedrine include Allegra-D, Alka-Seltzer Plus Cold Medicine Liqui-Gels, Aleve Cold and Sinus Caplets, Benadryl Allergy and Sinus Tablets, Claritin-D Non-Drowsy 24 Hour Tablets, Contac Non-Drowsy 12 Hour Cold Caplets, Robitussin Cold Severe Congestion Capsules, Sudafed 24 Hour Tablets, Triaminic Cold and Cough Liquid, Thera-Flu Cold and Cough Hot Liquid, Tylenol Sinus Severe Congestion Caplets, and Vicks 44M Cough, Cold and Flu Relief. Numerous case reports[3,4] in the literature suggest that oral sympathomimetic agents can raise blood pressure (BP) to dangerous levels, whereas other reviews[5,6] suggest that the danger from these medications is exaggerated. In November 2000, the US Food and Drug Administration recommended that medications that contain phenylpropanolamine be voluntarily recalled because of concern regarding an increased incidence of hemorrhagic stroke.[7] Markedly elevated BPs have been noted in conjunction with phenylpropanolamine-associated strokes, and hypertension has been suggested as a possible mechanism of drug toxicity.[8] Because physicians commonly prescribe pseudoephedrine to relieve the symptoms of the common cold, they speculate about its safety, particularly in patients with hypertension. In addition, because sympathomimetic agents can potentially elevate the heart rate (HR), safety issues also arise in patients with conditions such as atrial fibrillation, in which alterations in HR control could poten-

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Table 1. Characteristics of Studies of Pseudoephedrine That Included BP and HR Data

Source; Country (Study Design)	Focus of Study	Oral Drug Doses and Types	Patients, No.	Female Sex, %	Age, Mean (range), y	Trial Length	Quality Score (0-8)*	Quality Problems†	Extreme Hypertensive Responses
Backhouse et al,[15] 1990; England (parallel)‡	Treatment of allergic rhinitis	PSE (IR), 60 mg, tid PSE (IR), 60 mg, and TER, 40 mg, tid TER, 40 mg, tid	27 31 28	60	31	7 d	6	A	No mention of magnitude of individual BP changes
Beck et al,[16] 1992; United States (crossover)§	Effect on BP of hypertensive patients	PSE (SR), 120 mg, bid, vs placebo	28	39	63 (27-73)	3 d	8	NA	2 Individuals in each group with MAP increases >20 mm Hg
Bradley et al,[17] 1991; United States (parallel)§	Effect on BP in hypertensive patients	PSE (IR), 60 mg, qid Placebo	13 12	Unknown	(25-50)	3 d	6	A	5 Patients in treatment group and 6 in placebo group with BP >145/94 mm Hg
Bright et al,[18] 1981; United States (crossover)‡	Effect on BP during exercise	PSE (IR), 60 mg (1 dose), vs PSE (IR), 120 mg (1 dose), vs placebo	6	0	(23-28)	1 d	1	A, B, E, F	No mention of magnitude of individual BP changes
Britton et al,[19] 1978; England (crossover)‡	Effect on allergic rhinitis	PSE (IR), 60 mg (1 dose), vs TRI, 2.5 mg	10	Unknown	(24-35)	1 d	5	A, F	No mention of magnitude of individual BP changes
Bye et al,[20] 1974; England (crossover)‖	Effect on central nervous system	PSE (IR), 60 mg, vs PSE (IR), 120 mg, vs PSE (IR), 180 mg, vs ephedrine, 25 mg, vs ephedrine, 50 mg, vs placebo	12	8	(22-37)	7.5 h	5	A, D	No mention of magnitude of individual BP changes
Bye et al,[21] 1975; England (crossover)‖	Effect on BP and drug metabolism	PSE (IR), 180 mg, vs PSE (IR), 60 mg, tid, vs PSE (SR), 180 mg, vs PSE (SR), 180 mg, qd	10	50	(22-37)	1 d	6	B	No mention of magnitude of individual BP changes
Chua et al,[22] 1989; Australia (crossover)§	Effect on BP in hypertensive patients	PSE (IR), 60 mg, vs placebo	20	25	51 (31-71)	3.5 h	5	A, D	No mention of magnitude of individual BP changes
Clemons and Crosby,[23] 1993; United States (crossover)‡	Effect on BP during exercise	PSE (IR), 60 mg, vs placebo	10	100	20.4	1 d	5	A, F	No mention of magnitude of individual BP changes
Coates et al,[24] 1995; United States (crossover)§	Effect on BP of hypertensive patients	PSE (IR), 60 mg, tid, vs placebo	25	64	50.4 (31-68)	4 wk	8	NA	No mention of magnitude of individual BP changes
Dickerson et al,[25] 1978; United States (parallel)‡	Dose tolerance and pharmacokinetics	PSE (SR), 120 mg PSE (SR), 150 mg	16 17	0	25 (19-30)	1 wk	4	A, B	1 Subject stopped PSE owing to anxiety; DBP = 100 mm Hg and 25% increase in HR
Empey et al,[26] 1975; England (crossover)‡	Nasal and cardiovascular effects	PSE (IR), 15 mg, vs PSE (IR), 30 mg, vs PSE (IR), 60 mg, vs PSE (IR), 120 mg, vs PSE (IR), 180 mg	18	Unknown	(19-33)	140 min	6	A	1 Subject stopped PSE owing to anxiety and sinus tachycardia, changes deemed "clinically unimportant"

(*continued*)

tially result in harm. Our purpose is to conduct a systematic review of the literature to determine the effect of oral pseudoephedrine, used in adults, on HR and BP. Our a priori subgroup analytic questions included the following: Are the magnitude of changes on HR and BP affected by patient characteristics, such as age, sex, and currently treated hypertension, or by drug characteristics, such as extended- or immediate-release formulations, dose, and treatment duration?

METHODS

For this review, we searched MEDLINE (1966-2005) and EMBASE (1974-2005) for clinical trials on adults using the medical subject heading term *pseudoephedrine* combined with the text words *hypertension, blood pressure, heart rate, adverse effects,* and *clinical trial*. We also searched the Cochrane Library (the Clinical Trials Registry for randomized trials and the Cochrane Database of Systematic Reviews for systematic reviews). All references of reviewed articles were scrutinized for additional articles missed by the computerized database search. All articles that were identified as randomized controlled trials in either the title or the abstract were further screened by review of the full article. This screening was necessary because trials on the effectiveness of the preparations on weight loss or on cold symptoms often included extractable data on the effect of the preparations on vital signs without mentioning that fact in either the title or the abstract. We screened articles based on the following criteria: randomization, placebo control, at least 1 group receiving a sympathomimetic medication, and extractable outcomes reported.

Included study quality was assessed using a 6-item instrument developed and validated by Jadad et al.[9] The 6 items in the Jadad scale include description of randomization, adequacy of blinding, description of withdrawals and dropouts, appropriateness of statistical analysis, description of inclusion and exclusion criteria, and method of assessing adverse treatment effects. Jadad study quality was assessed independently by 2 reviewers (S.M.S. and E.P.B.), with substantial interrater agreement ($\kappa = 0.84$). Disagreements were arbitrated by consensus.

Abstracted data included setting, country of origin, treatment characteristics (dose, duration, type of formulation, and type of study), demographics, number of participants enrolled, follow-up losses, adverse effects, and the outcomes of systolic BP (SBP), diastolic BP (DBP), and

Table 1. Characteristics of Studies of Pseudoephedrine That Included BP and HR Data (cont)

Source; Country (Study Design)	Focus of Study	Oral Drug Doses and Types	Patients, No.	Female Sex, %	Age, mean (range), y	Trial Length	Quality Score (0-8)*	Quality Problems†	Extreme Hypertensive Responses
Henauer et al,[27] 1991; Switzerland and England (parallel)‖	Treatment of allergic rhinitis	PSE (SR) with TER, 60 mg, bid	25	58	31	2 wk	8	NA	No mention of magnitude of individual BP changes
		TER, 60 mg,bid	25						
Hendershot et al,[28] 2001;United States (crossover)‖	Interaction with linezolid	PSE (IR), 25 mg, every 4 h × 2 vs placebo with or without linezolid	42	Unknown	(18-35)	9 d	6	A	No mention of magnitude of individual BP changes
Higgins et al,[38] 1979; United States (crossover)‡	Decongestants and altitude	PSE (IR), 60 mg, vs placebo	14	0	(18-33)	3 h	6	A	No mention of magnitude of individual BP changes
Janssens and Lins,[29] 1995; Belgium (parallel)‖	Effect of astemizole-D on sleep	PSE (SR), 240 mg, with astemizole, 10 mg	120	55	33.2 (18-56)	3 d	6	A	No mention of magnitude of individual BP changes
		PSE (SR), 120 mg, with loratadine, 5 mg	120						
Laitinen et al,[30] 1982; Finland (crossover)‡	Treatment of asthma	PSE (IR), 60 mg, vs PSE (IR), 180 mg	12	Unknown	<45	2 h	5	A, F	No mention of magnitude of individual BP changes
Mores et al,[31] 1999; Italy (crossover)§	Effect on BP in patients taking β-blockers	PSE (IR), 60 mg, and placebo vs PSE (IR), 60 mg, and propranolol, 160 mg, vs PSE (IR), 60 mg, and atenolol, 100 mg	29	38	49	2 h	2	A, B, F	No mention of magnitude of individual BP changes
Negrini et al,[32] 1995; Belgium, Italy, Austria, and Germany (parallel)‖	Treatment of allergic rhinitis	PSE (SR), 240 mg/astemizole, 10 mg, qd plus placebo spray bid	102	46	28.2 (12-66)	4 wk	6	A	No mention of magnitude of individual BP changes
		Beclomethasone, 0.05 mg bid, spray plus placebo pill	102						
Perkins et al,[37] 1980; United States (crossover)‡	Bioavailability and drug metabolism	PSE (IR), 60 mg/TRI, 2.5 mg, vs PSE (SR), 120 mg/TRI, 5.0 mg, vs placebo	18	50	27.5 (21-39)	5 d	6	A	No mention of magnitude of individual BP changes
Rosene et al,[36] 1999; United States (crossover)‡	Effect on BP during exercise	PSE (SR), 120 mg bid, vs placebo	10	0	22.3	3 d	4	A, E, F	No mention of magnitude of individual BP changes
Sperber et al,[35] 1989; United States (parallel)‖	Treatment of rhinovirus cold	PSE (IR), 60 mg qid	23	45	20	5 d	6	A	No mention of magnitude of individual BP changes
		PSE (IR), 60 mg/ibuprofen, 200 mg qid	23						
		Placebo	10						
Stroh et al,[34] 1988; United States (parallel)‡	Treatment of allergic rhinitis	PSE (SR), 120 mg bid	158	55	31 (12-74)	2 wk	3	A, B, F	16 Patients had SBP >139 mm Hg and 19 had DBP >89 mm Hg while taking PSE-containing treatments
		PSE (SR), 120 mg/TER, 60 mg bid	159						
Swain et al,[33] 1997; United States (crossover)‡	Effects on BP during exercise	PSE (IR), 1 mg/kg, vs PSE (IR), 2 mg/kg	10	0	27.1	1 d	6	A	No mention of magnitude of individual BP changes

Abbreviations: bid, twice daily; BP, blood pressure; BPA, brompheniramine; DBP, diastolic BP; HR, heart rate; IR, immediate release; MAP, mean arterial pressure; PSE, pseudoephedrine; qd, every day; qid, 4 times daily; SBP, systolic BP; SR, sustained release; TER, terfenadine; tid, 3 times daily; TRI, triprolidine.

*Quality score developed and validated by Jadad et al.[9]

†A indicates poor description of randomization technique; B, lack of description of blinding or identical placebo; C, failure to adequately describe withdrawals; D, failure to describe statistical analysis; E, no detailed inclusion and exclusion criteria; F, failure to describe method of assessing adverse advents; and NA, not applicable.

‡Patients with hypertension were not included.

§Patients with hypertension were included.

‖Unknown if patients with hypertension were included.

HR. All outcomes were extracted as continuous variables.

Analyses were performed using a statistical software program (Stata 8; StataCorp, College Station, Tex). Assessment for publication bias was performed using the methods of Egger et al[10]; heterogeneity was assessed visually using Galbraith plots and Q (χ^2) statistics using the Mantel-Haenzel test.[11] The random-effects model of DerSimonian and Laird[12] was used to calculate summary weighted mean differences. Analysis of outcomes involved comparing weighted mean differences between control and treatment groups for all sympathomimetic drugs and several subgroups of studies. These subgroup analyses included probing for differences between extended- and immediate-release preparations of each drug, short-term (<1 day) and long-term administration of drugs, low and high (>60 mg pseudoephedrine) doses of medications, patients with and without hypertension, and studies that did and did not include women. Further analyses were per-

formed to determine whether results differed between high- and low-quality (Jadad score <6) studies and studies that specifically included baseline BP readings immediately before administration of the treatment or placebo medication.

Several measures of the sensitivity of the meta-analysis results to various assumptions were conducted. If publication bias was found, we calculated its potential impact using the "trim-and-fill" method of Duval and Tweedie.[13] We also investigated the effect of any single study on the results by sequentially removing studies, one at a time, and reanalyzing the results. We also explored several sources of heterogeneity, including year of publication, type of medication, inclusion of multiple sexes, length of studies, and study quality scores using meta-regression[14] and stratified analyses. Finally, we assessed the normality of the distribution of the results using the Shapiro-Wilks test of normality to assess whether including multiple arms from single studies distorted the expected normality of effect.

RESULTS

STUDY SELECTION

A total of 859 studies were found in the initial broad search. Of these studies, only 153 contained topic matter on oral pseudoephedrine and were not obviously case reports. Another 129 studies were eliminated because they were not adult trials (n=5), were not English-language trials (n=6), did not collect vital signs in their methods (n=80), reported vital sign data only as "no change" (n=21), and were not randomized placebo-controlled trials (n=16) and for other miscellaneous reasons (n=1). The final list of included articles comprised 24 studies with 45 treatment arms (**Table 1**).[15-38]

STUDY CHARACTERISTICS

The 24 studies included 1285 patients. Thirty-one arms used immediate-release formulations and 14 arms used sustained-release formulations. Doses ranged from 15 to 240 mg. Studies came from 9 different countries (Australia, Switzerland, United States, England, Italy, Austria, Germany, Belgium, and Finland). Sixteen studies were crossover trials, and 8 used parallel groups. The 15 crossover trials that reported washout periods in their methods averaged 7.2 washout days between treatments (range, 1-14 days). The mean study duration was 4.6 days (range, 1-28 days), and the mean patient age was 34.9 years (range, 20-63 years). Overall, 34% of the patients were women, with 6 studies including only men and 1 including only women. Five trials with 7 treatment arms investigated the effects of pseudoephedrine treatment in patients with stable, treated hypertension, and 4 studies with 5 treatment arms investigated the effects on exercise. The mean±SD Jadad quality score of the assembled articles was 5.9±1.7.

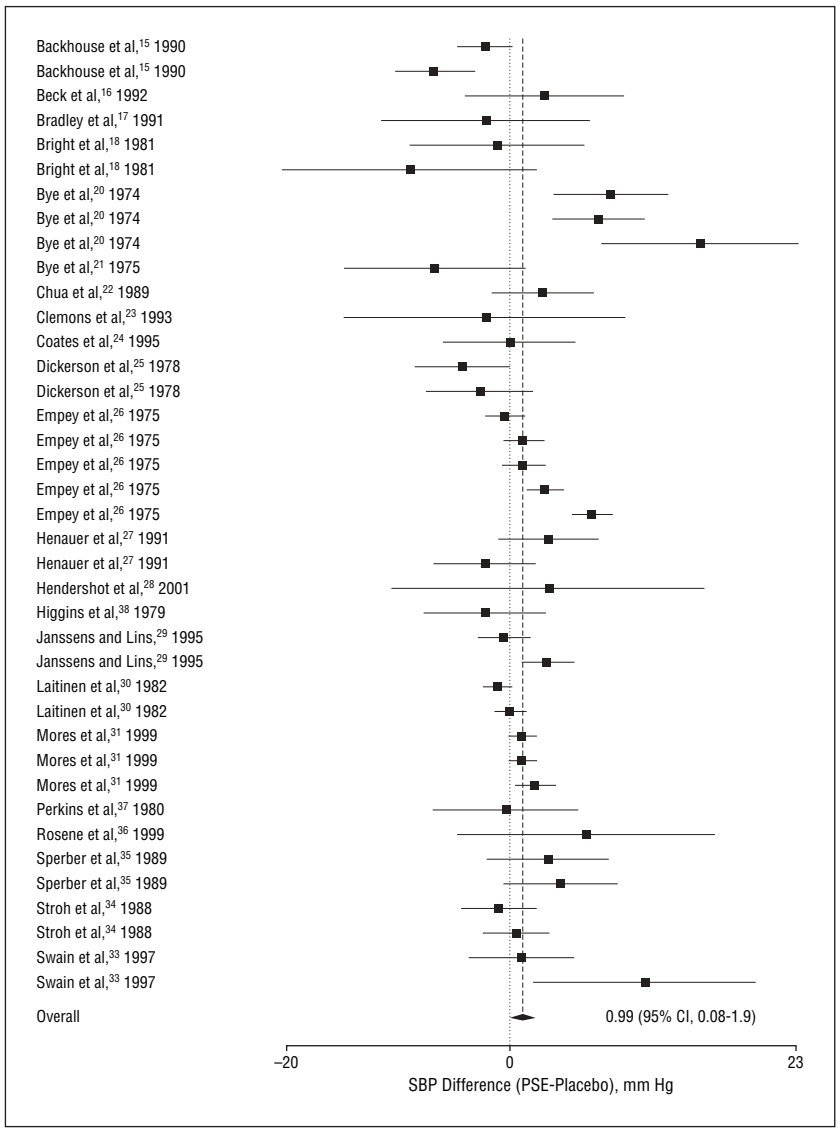

Figure 1. Effect of pseudoephedrine (PSE) on systolic blood pressure (SBP). Data are given as mean (95% confidence interval [CI]).

EFFECT ON BP AND HR

Pseudoephedrine caused a slight but significant increase in SBP (0.99 mm Hg; 95% confidence interval [CI], 0.08-1.90 mm Hg) (**Figure 1**) and HR (2.83 beats/min; 95% CI, 2.03-3.63 beats/min) (**Figure 2**), with no significant effect on DBP (0.63 mm Hg; 95% CI, –0.10 to 1.35 mm Hg) (**Figure 3** and **Table 2**). The immediate-release formulations significantly elevated the SBP (1.53 mm Hg; 95% CI, 0.49-2.56 mm Hg), whereas the sustained-release formulations had no effect (–0.98 mm Hg; 95% CI, –2.44 to 0.47 mm Hg) (Table 2). Neither immediate-release nor extended-release formulations significantly

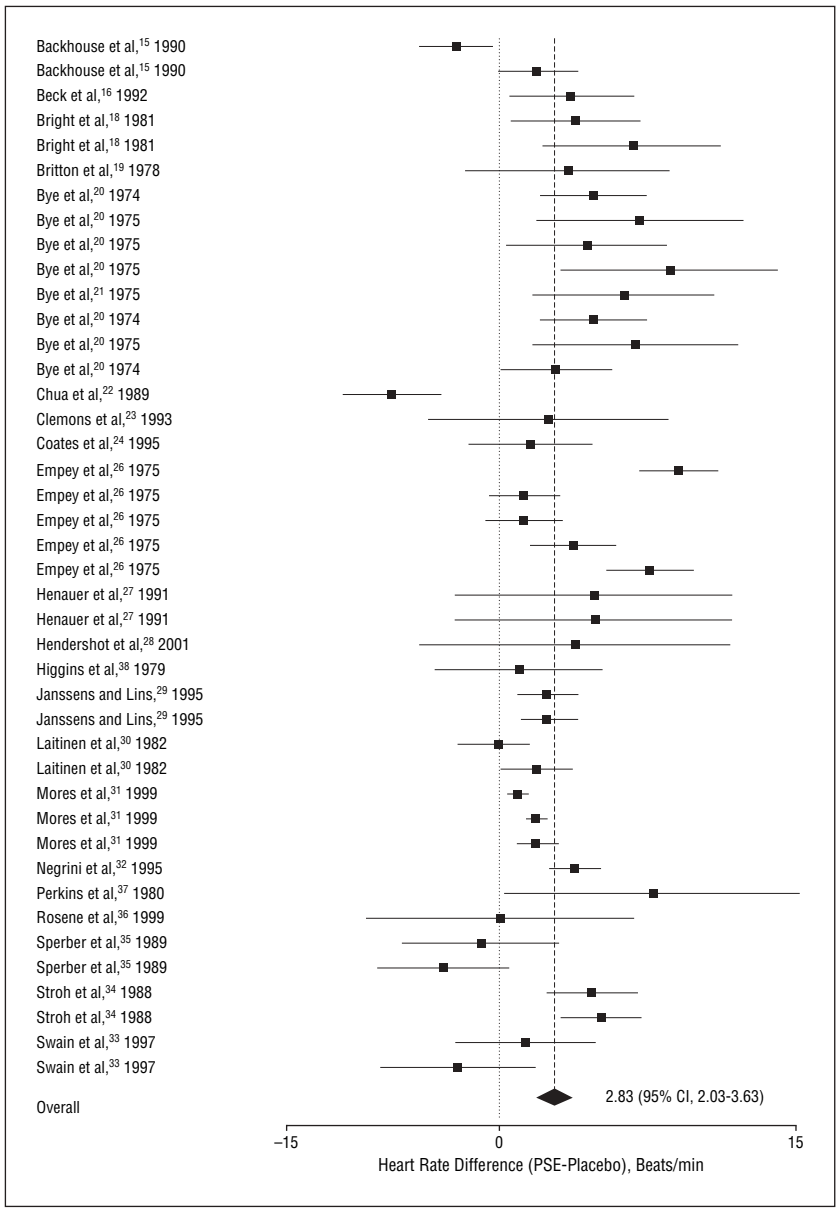

Figure 2. Effect of pseudoephedrine (PSE) on heart rate. Data are given as mean (95% confidence interval [CI]).

increased DBP. Heart rate was significantly elevated with use of the immediate-release (2.3 beats/min, 95% CI, 1.42-3.19 beats/min) and extended-release (4.48/min; 95% CI, 3.31-5.64 beats/min) formulations. With the immediate-release formulations, there was a dose-response relationship for SBP, DBP, and HR ($P<.001$ for all). An example of the dose-response relationship for SBP with the immediate-release formulations is depicted in **Figure 4**. Longer study duration was associated with less of an effect on SBP (**Figure 5**), but there was no relationship between duration of exposure to pseudoephedrine and either DBP or HR effects. Studies with more women demonstrated less effect with pseudoephedrine use on all 3 cardiovascular variables. The impact of female sex on SBP is demonstrated in **Figure 6**.

Seven treatment arms composed of patients with known, stable, treated hypertension examined the effect of pseudoephedrine. Slight, comparable elevations in SBP (1.2 mm Hg; 95% CI, 0.56-1.84 mm Hg), DBP (0.55 mm Hg; 95% CI, –1.17 to 2.27 mm Hg), and HR (0.95 beats/min; 95% CI, –0.31 to 2.21 beats/min) were found, although they achieved statistical significance only for SBP ($P<.001$) (Table 2). There were no significant effects on vital signs in patients who underwent exercise testing (Table 2). There were no effects of age, country or year of study, study design, or duration of washout on our results. Our results were not overly affected by the inclusion of any single study because analyses conducted by sequentially excluding single studies did not significantly change the outcomes. In addition, the reported effects on SBP ($P=.13$), DBP ($P=.10$), and HR ($P=.78$) were normally distributed, reassuring that including multiple arms from a single study did not introduce bias in the expected normal distribution of outcomes.

There was no evidence of publication bias for SBP or DBP, although there was evidence of bias in the HR results (**Table 3**). Adjustment for potential publication bias using the trim-and-fill method reduced the increase in HR with pseudoephedrine from 3.4 beats/min to 1.7 beats/min (95% CI, 0.9-2.6 beats/min).

We searched for more extreme effects of pseudoephedrine treatment and found that in the 24 studies involving 1108 patients exposed, 2 patients experienced mean arterial pressure elevations of 20 mm Hg; 5 treated, hypertensive patients had BPs greater than 145/94 mm Hg; 19 patients had a DBP greater than 89 mm Hg; 16 had an SBP greater than 139 mm Hg; 1 reported anxiety, a DBP of 100 mm Hg, and a 25% increase in HR; and 1 reported anxiety and sinus tachycardia. In most of these studies, there is no description of baseline BP before medication administration, and in many, the placebo group also showed BP elevations. In the cases that described elevated HR, the absolute magnitude also was not described.

COMMENT

This analysis demonstrates that pseudoephedrine causes a small but significant mean (1–mm Hg) increase in SBP, with no significant effect on DBP and a slight increase in HR (3 beats/min). Immediate-release formulations had a greater

effect than sustained-release medications. Among immediate-release formulations, there was a dose-response relationship for all 3 cardiovascular variables. Women seemed to be less susceptible to the cardiovascular effects than men; the higher the proportion of women in each study, the lower were the effects found.

This review found a dose-response relationship between the magnitude of the drug dose and the effect on BP. More substantial elevations of SBP and DBP were noted with higher doses of medication. In patients with stable, treated hypertension, pseudoephedrine therapy increased the SBP but had no effect on HR or DBP. The neutral effect on HR observed in hypertensive patients is likely to be attributed to the 4 study arms that included patients receiving β-adrenergic blockade.

There was no documentation of any clinically significant adverse outcomes. However, a rare event, such as an idiosyncratic extreme reaction to a sympathomimetic agent, may not be seen with this small (N=1260) sample size. Adverse effects, such as hypertensive strokes, have been attributed to pseudoephedrine in the literature in several cases.[8] Although we found no serious adverse effects in these randomized trials, we observed 30 reported episodes of hypertension to levels greater than 140/90 mm Hg among the 1108 exposed patients. It was not reported whether these episodes were clinically important, what the baseline BP was, or what their magnitude was in most of the individual patients affected. We also do not know whether many of these patients were taking other medications, such as nonsteroidal anti-inflammatory drugs, that may have affected BP levels.

It is possible that patients with exaggerated hypertensive responses have a degree of underlying autonomic instability. Biaggioni and colleagues[39] demonstrated exaggerated BP responses (mean SBP increase, 32 mm Hg) in 14 patients with autonomic failure and orthostatic hypertension exposed to phenylpropanolamine. It is possible that a pharmacodynamic difference in receptor sensitivity or expression may be a factor. This idea is supported by 1 trial[40] that demonstrated significant BP variability in response to intravenous phenylpropanolamine in nonobese individuals without postural hypotension or autonomic impairment. Future research might examine subsets of the population at

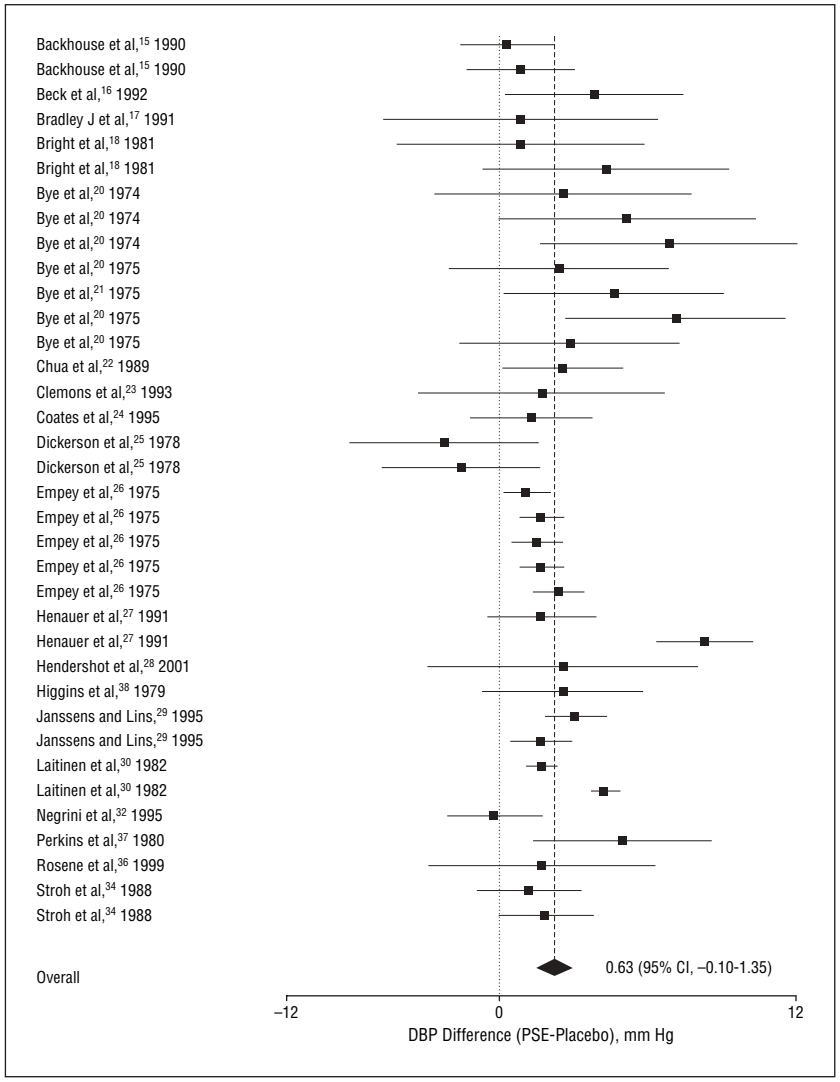

Figure 3. Effect of pseudoephedrine (PSE) on diastolic blood pressure (DBP). Data are given as mean (95% confidence interval [CI]).

Table 2. Effect of Pseudoephedrine Therapy on Vital Signs*

Variable	Treatment Arms, No.	SBP, mm Hg	DBP, mm Hg	Heart Rate, Beats/min
All pseudoephedrine study arms	45	0.99 (0.08 to 1.90)	0.63 (–0.10 to 1.35)	2.83 (2.03 to 3.63)
Studies with hypertensive patients	7	1.20 (0.56 to 1.84)	0.55 (–1.17 to 2.27)	0.95 (–0.31 to 2.21)
Immediate-release preparation	31	1.53 (0.49 to 2.56)	0.38 (–0.37 to 1.13)	2.30 (1.42 to 3.19)
Sustained-release preparation	14	–0.98 (–2.44 to 0.47)	0.97 (–1.39 to 3.33)	4.48 (3.31 to 5.64)
Studies with exercising patients	5	–0.24 (–3.64 to 3.15)	1.28 (–1.14 to 3.71)	2.50 (–2.00 to 7.01)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
*Data are given as weighted mean difference (95% confidence interval) in mean pooled vital signs in placebo-treated and active therapy individuals compared with vital signs after treatment.

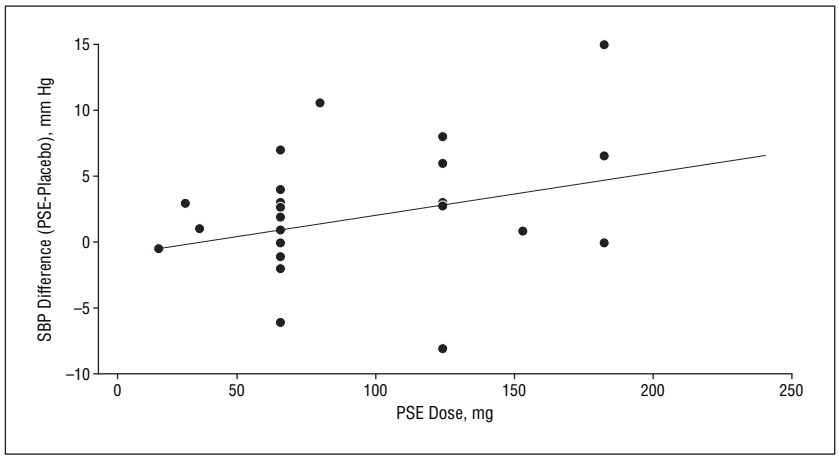

Figure 4. Relationship between systolic blood pressure (SBP) and pseudoephedrine (PSE) dose. Each dot represents an individual study; diagonal lines, meta-regression lines.

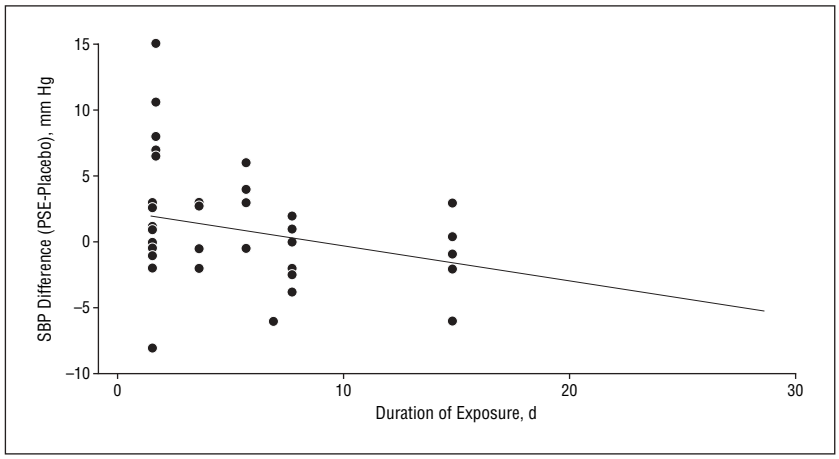

Figure 5. Impact of exposure duration on systolic blood pressure (SBP) elevation in patients receiving pseudoephedrine (PSE). Each dot represents an individual study; diagonal lines, meta-regression lines.

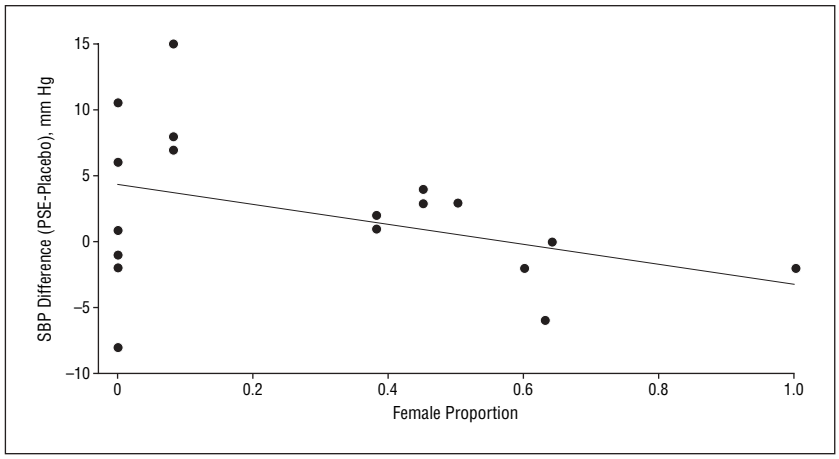

Figure 6. Impact of female sex on systolic blood pressure (SBP) elevation in patients receiving pseudoephedrine (PSE). Each dot represents an individual study; diagonal lines, meta-regression lines.

risk for autonomic insufficiency, such as diabetic patients, to determine whether exaggerated BP responses to oral pseudoephedrine are present. Although few patients had extreme elevations in BP, many individual patients had changes, raising the BP from low normal to high normal or slightly hypertensive levels. Given the uncommon description of adverse effects in the studies we reviewed, it is unlikely that these changes are of clinical significance to most patients.

We were also interested in whether the normal elevation of BP and HR during exercise was accentuated by pseudoephedrine. The medication did not produce significant increases in BP or HR with exercise above the levels in those not exposed to pseudoephedrine in the young, healthy population studied.

This study had several limitations. First, the population studied included an insufficient number of older patients to reach conclusions on use in the elderly population. Second, we evaluated only 1 element of safety—BP and HR. Pseudoephedrine may have many other adverse effects, such as drug-drug interactions, that are beyond the scope of this article. Many of the included studies pooled baseline vital sign data for placebo and treatment groups. Separate analysis of studies with separate baseline data for both groups, and higher-quality studies in general, showed less pronounced effects on vital signs. Therefore, we may have overestimated the effect of pseudoephedrine in our results. However, we believed it was important to highlight the worst-case scenario for patients, and we chose to include the lesser-quality studies. In addition, the studies reported mean BP and HR responses rather than individual data. Mean results may mask extreme responses. If 40 individuals had only a 1– or 2–mm Hg increase in SBP but 1 increased BP by 30 mm Hg, this would still yield an average response of only 1 to 2 mm Hg. Some studies included a statement that no participant had a marked increase in BP, but most provided no information. Moreover, our total study sample size was 1260 patients, which may be too small to detect rare idiosyncratic adverse events. The emergence of a risk of hemorrhagic stroke and marked BP elevation in postmarketing surveillance with phenylpropanolamine was seen in only a few cases when the total number of prescriptions in the general population was in the millions. Our data cannot be used to fully eliminate the possibility of this risk. In addition, we may have experienced publication bias. There were 21 additional

Table 3. Tests of Heterogeneity and Publication Bias

Outcome	Treatment Arms, No.	*P* Value	
		Heterogeneity*	Publication Bias†
Systolic blood pressure	39	<.001	.88
Diastolic blood pressure	36	<.001	.82
Heart rate	42	<.001	.06

*χ^2 Test; $P<.10$ indicates heterogeneity of the effect size between studies.
†Egger test; $P<.10$ indicates bias against small studies with negative findings.

randomized controlled trials that reported "no effect" on HR or BP on exposure to pseudoephedrine. It is likely that studies may have been more likely to report their data when an effect was seen. If so, then our analysis would tend to overstate the mean magnitude of effect.

We conclude that pseudoephedrine modestly increases SBP and HR. These effects are greatest in magnitude with immediate-release formulations, higher doses of medication, and short-term medication administration. Patients with stable, controlled hypertension do not seem to be at higher risk for BP elevation as a group than other patients when given pseudoephedrine along with their antihypertensive medications. Effects of pseudoephedrine may be important when considered on a population basis given their widespread use as decongestants. Although we did not find any life-threatening adverse effects of BP elevation in this review, a meta-analysis cannot predict how any individual patient will react. Although marked elevations of BP were uncommon in patients included in this meta-analysis, elevations in BP greater than 140/90 mm Hg were present in nearly 3% of the patients studied. Therefore, the risk-benefit ratio should be evaluated carefully before using sympathomimetic agents in individual patients most at risk for BP and HR elevations. We encourage physicians to instruct patients with cardiovascular disease to monitor their BP carefully after starting therapy.

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