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PHENYLPROPANOLAMINE AND THE RISK OF HEMORRHAGIC STROKE

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ABSTRACT

Background Phenylpropanolamine is commonly found in appetite suppressants and cough or cold remedies. Case reports have linked the use of products containing phenylpropanolamine to hemorrhagic stroke, often after the first use of these products. To study the association, we designed a case–control study.

Methods Men and women 18 to 49 years of age were recruited from 43 U.S. hospitals. Eligibility criteria included the occurrence of a subarachnoid or intracerebral hemorrhage within 30 days before enrollment and the absence of a previously diagnosed brain lesion. Random-digit dialing identified two matched control subjects per patient.

Results There were 702 patients and 1376 control subjects. For women, the adjusted odds ratio was 16.58 (95 percent confidence interval, 1.51 to 182.21; P=0.02) for the association between the use of appetite suppressants containing phenylpropanolamine and the risk of a hemorrhagic stroke and 3.13 (95 percent confidence interval, 0.86 to 11.46; P=0.08) for the association with the first use of a product containing phenylpropanolamine. All first uses of phenylpropanolamine involved cough or cold remedies. For men and women combined, the adjusted odds ratio was 1.49 (95 percent confidence interval, 0.84 to 2.64; P=0.17) for the association between the use of a product containing phenylpropanolamine and the risk of a hemorrhagic stroke, 1.23 (95 percent confidence interval, 0.68 to 2.24; P=0.49) for the association with the use of cough or cold remedies that contained phenylpropanolamine, and 15.92 (95 percent confidence interval, 1.38 to 184.13; P=0.03) for the association with the use of appetite suppressants that contained phenylpropanolamine. An analysis in men showed no increased risk of a hemorrhagic stroke in association with the use of cough or cold remedies containing phenylpropanolamine. No men reported the use of appetite suppressants.

Conclusions The results suggest that phenylpropanolamine in appetite suppressants, and possibly in cough and cold remedies, is an independent risk factor for hemorrhagic stroke in women. (N Engl J Med 2000;343:1826-32.)

PHENYLPROPANOLAMINE is a synthetic sympathomimetic amine commonly found in appetite suppressants and cough and cold remedies. Each month, millions of Americans use products containing phenylpropanolamine. Since 1979, more than 30 case reports have been published that describe the occurrence of intracranial hemorrhage after the ingestion of phenylpropanolamine.[1-9] Affected patients were most commonly adolescent girls or young women between the ages of 17 and 45 years who were using phenylpropanolamine-containing appetite suppressants, often for the first time.[7-13] In addition to the published reports, between 1969 and 1991, the Food and Drug Administration (FDA) received 22 spontaneous reports of hemorrhagic stroke associated with phenylpropanolamine in appetite suppressants (in 16 cases) or cough and cold remedies (in 6 cases) (Jolson HM: personal communication).

In response to the concern aroused by these case reports, in 1992 we collaborated with the FDA and manufacturers of phenylpropanolamine to design the Hemorrhagic Stroke Project, a case–control study of men and women who were 18 to 49 years of age. The study had three prespecified aims: to estimate, among women, the association between hemorrhagic stroke and the use of appetite suppressants containing phenylpropanolamine and any first use of products containing phenylpropanolamine; to estimate, among men and women, the association between any use of phenylpropanolamine in either an appetitie suppressant or a cough or cold remedy and hemorrhagic stroke; and to estimate, among men and women, the

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association between hemorrhagic stroke and the type of exposure to phenylpropanolamine.

METHODS

Recruitment and Classification of Patients with Hemorrhagic Stroke

Between December 1994 and July 1999, we identified patients with symptomatic subarachnoid or intracerebral hemorrhage from 43 hospitals in Connecticut, Massachusetts, Ohio, Kentucky, Rhode Island, and Texas (see the Appendix). A subarachnoid hemorrhage was diagnosed on the basis of clinical symptoms plus either evidence of subarachnoid bleeding on computed tomography (CT) or evidence of xanthochromia on lumbar puncture. An intracranial hemorrhage was diagnosed on the basis of clinical symptoms plus a CT or magnetic resonance imaging scan showing blood primarily in the parenchyma of the brain. Eligibility criteria for patients included an age of 18 to 49 years, the ability to communicate and complete the interview within 30 days after the stroke, the absence of a history of a brain lesion that would increase the risk of hemorrhage (i.e., an arteriovenous malformation, tumor, or aneurysm), and the absence of a history of stroke. Patients were recruited in person or by telephone as soon as they were identified, provided that their personal physician approved.

Recruitment of Control Subjects

We attempted to identify two matched control subjects for each patient through the use of random-digit dialing. Matching criteria included telephone exchange, sex, race (black or nonblack), and age (within 3 years in the case of patients who were younger than 30 years of age and within 5 years in the case of patients who were 30 or older). When a perfectly matched control could not be located, we enrolled an imperfectly matched control rather than excluded the patient from the study. All interviews with control subjects had to be completed within 30 days after the patient's stroke to minimize seasonal differences in exposure to products containing phenylpropanolamine.

Definition of Focal Time

For each patient, we identified the focal time, which we defined as the calendar day (i.e., the index day) and the time of day that marked the onset of symptoms that were plausibly related to hemorrhage and that caused the patient to seek medical attention. Some patients with subarachnoid or intracerebral hemorrhage may have a transient headache hours or days before the onset of symptoms that lead them to seek medical attention.[14,15] The cause of these sentinel headaches is not known, although clinicians infer that some may be due to minor bleeding.[16] Accordingly, for patients with such headaches we defined a modified focal time as the time of onset of the sentinel headache. We used this definition in a secondary analysis.

The focal time used for each control subject was matched to the day of the week and the time of day that corresponded to the patient's focal time. We interviewed the control subject within seven days after this date, to improve recall of exposures and thereby minimize the opportunity for recall bias.

Ascertainment of Data on Exposure and Other Information

Trained researchers used a structured questionnaire to obtain demographic, clinical, behavioral, and pharmaceutical information from all subjects. Interviews were conducted in person unless the subject refused or a meeting could not be arranged within 30 days after the focal time in the patients (in which case the interview took place by telephone). Subjects were asked to recall cold symptoms, medications used to treat them, and any other medications taken during the two weeks before the focal time. After all such responses had been recorded, subjects were asked whether they had taken several specific medications or classes of medications (e.g., aspirin, anticoagulants, and diet pills).

To verify information about exposure to medications, subjects were asked to pick out brand-name medications from a book containing photographs of packages. They were then asked to produce each medication so that the exact name and manufacturer's lot number could be recorded. If the container was not available, use of a brand-name medication was considered verified if the subject identified it in the book. Only verified exposures to medication were counted in the analysis.

To determine the active ingredients in each medication, we relied on published sources.[17,18] For national brands and prescription drugs that may have had changes in formulation during the study period and for generic or store-brand medications, we verified active ingredients directly with the manufacturer.

Definition of Exposure to Phenylpropanolamine

The window of exposure to phenylpropanolamine refers to the interval before the focal time when a subject's exposure status is defined. For all analyses except those involving the first use of a product containing phenylpropanolamine, the window of exposure was defined as the index day before the focal time and the preceding three calendar days. For the first use of a product containing phenylpropanolamine, a subject was considered to have been exposed if he or she had used a product containing phenylpropanolamine within 24 hours before the focal time and had not used any other such products during the preceding two weeks. To maintain a consistent reference group, nonexposure for all analyses was defined by the absence of the use of products containing phenylpropanolamine within two weeks before the focal time.

Statistical Analysis

The sample size was based on the need to determine whether the first use of products containing phenylpropanolamine increased the risk of hemorrhagic stroke among women who were 18 to 49 years of age. Using available market data, we estimated that 0.502 percent of control subjects would report an exposure to phenylpropanolamine within 24 hours before the focal time. We specified one-tailed statistical tests because the focus of this research was the effect of phenylpropanolamine in increasing the risk of stroke. For a one-tailed test of significance at the 0.05 level and for the study to have a power of 80 percent to detect among women an odds ratio of 5.0 for hemorrhagic stroke after the first use of a product containing phenylpropanolamine, 324 female patients and 648 female control subjects were required. Because our research interest extended to the effects of phenylpropanolamine in men, we doubled our sample size to include 350 male and 350 female patients and 1400 controls.

In the first phase of the analysis, we compared demographic and clinical features of patients and control subjects using the chi-square test or Fisher's exact test (SAS Institute, Cary, N.C.). In the second phase, we estimated odds ratios and 95 percent confidence intervals for the association between hemorrhagic stroke and exposure to phenylpropanolamine using conditional logistic models for matched sets. Because of the low incidence rate of hemorrhagic stroke, the odds ratio is a close approximation of the relative risk. We calculated unadjusted and adjusted estimates using exact methods and asymptotic methods, respectively. We adjusted for black race (because not all patients and control subjects were successfully matched for this factor), presence or absence of a history of hypertension, and current smoking status. We also adjusted for features that, when added to this model, changed the matched odds ratio by at least 10 percent. All logistic models were estimated with use of the LogXact Program (version 2.1, Cytel Software, Cambridge, Mass.). Although we used a one-sided test of significance at the 0.05 level to estimate sample size, for the results we present two-sided P values and 95 percent confidence intervals.

An autonomous external scientific advisory group reviewed the protocol and research progress, developed criteria for early termination, and evaluated interim and final analyses. Two interim analyses of the data were conducted. Because of the (conservative) O'Brien–Fleming spending function we used to assess the asso-

ciations between phenylpropanolamine use and hemorrhagic stroke during the interim analyses, no adjustment has been made in the P values and confidence intervals computed with all the data and presented in this report.

RESULTS

Study Participants

Between December 1994 and July 1999, 1714 patients with hemorrhagic stroke were identified (Table 1). Among these, 784 patients were ineligible for enrollment, 222 were eligible but were not enrolled, and 708 were enrolled. Six of those who were enrolled were not included in the analysis: there were no matched control subjects for three, two were interviewed more than 30 days after the stroke, and in the case of one patient the index day could not be determined. Thus, the analysis included 702 patients: 425 (61 percent) had had a subarachnoid hemorrhage and 277 (39 percent) had had an intracerebral hemorrhage.

A total of 674 patients (96 percent) had two matched control subjects apiece, and 28 patients (4 percent) each had one matched control subject. All control subjects were matched to their respective patients for sex and telephone exchange. Age matching was successful in the case of 1367 controls (99 percent), and 1321 controls (96 percent) were matched for race. On average, for each patient, we called 151 telephone numbers (range, 3 to 1119) and identified 2.8 eligible persons (range, 1 to 12) for each control enrolled.

As compared with control subjects, patients were significantly ($P<0.05$) more likely to be black and to report lower levels of education, current cigarette smoking, a history of hypertension, a family history of hemorrhagic stroke, regular alcohol use (more than two drinks per day), and recent cocaine use (Table 2). Patients were less likely to report the use of nonsteroidal antiinflammatory drugs and more likely to report the use of pharmaceutical agents that contained caffeine and nicotine (Table 3).

To identify variables for inclusion in multivariable models, we sequentially tested each feature listed in Table 2 and Table 3 in the basic model, which included race (black vs. nonblack), presence or absence of hypertension, and current smoking status. Under any definition of exposure to phenylpropanolamine, only the level of education changed the adjusted odds ratio for the association with hemorrhagic stroke by more than 10 percent.

Association between Phenylpropanolamine and Hemorrhagic Stroke

Table 4 shows the results of analyses of the relation between the use of products containing phenylpropanolamine and the risk of hemorrhagic stroke for women and men separately and for all subjects combined. Frequencies are shown in an unmatched format for patients and control subjects, with adjusted matched odds ratios provided.

TABLE 1. IDENTIFICATION AND ENROLLMENT OF PATIENTS.*

GROUP	NO. OF PATIENTS
Ineligible patients	784
Died within 30 days after stroke	389
Not able to communicate within 30 days after stroke	194
History of stroke	120
History of brain tumor or arteriovenous malformation	48
Hospitalized >72 hr before stroke occurred	33
Eligible patients	930
Not enrolled†	222
Not contacted within 30 days after stroke	182
Declined to participate	37
Approval to contact patient not granted by treating physician	3
Enrolled	708

*A total of 1714 patients were identified who had a hemorrhagic stroke between December 1994 and July 1999.

†In the case of eligible patients who were not enrolled, their ability to communicate within 30 days after the event was not assessed.

For women, analysis of the association between the use of phenylpropanolamine in appetite suppressants within three days before the focal time and the risk of hemorrhagic stroke yielded an adjusted odds ratio of 16.58 (95 percent confidence interval, 1.51 to 182.21; $P=0.02$). With respect to the risk of a hemorrhagic stroke after the first use of a product containing phenylpropanolamine, the adjusted odds ratio was 3.13 (95 percent confidence interval, 0.86 to 11.46; $P=0.08$). All first uses of a product containing phenylpropanolamine involved cough or cold remedies.

For men and women combined, analysis of the association between any use of a product containing phenylpropanolamine within three days before the focal time and the risk of a hemorrhagic stroke yielded an adjusted odds ratio of 1.49 (95 percent confidence interval, 0.84 to 2.64; $P=0.17$). With respect to the risk of a hemorrhagic stroke within three days after the use of a cough or cold remedy containing phenylpropanolamine, the adjusted odds ratio was 1.23 (95 percent confidence interval, 0.68 to 2.24; $P=0.49$), and for the risk associated with the use of an appetite suppressant containing phenylpropanolamine within three days before the focal time, the adjusted odds ratio was 15.92 (95 percent confidence interval, 1.38 to 184.13; $P=0.03$).

The results of the analyses shown in Table 4 indicate that with respect to the use of cough or cold remedies containing phenylpropanolamine, the adjusted odds ratio for the risk of a hemorrhagic stroke

TABLE 2. CHARACTERISTICS OF THE PATIENTS AND THE CONTROL SUBJECTS.

CHARACTERISTIC	PATIENTS (N=702)*	CONTROLS (N=1376)	P VALUE
	number (percent)		
Female sex	383 (55)	750 (55)	0.98
Black race	146 (21)	232 (17)	0.03
Age			0.74
<40 yr	296 (42)	592 (43)	
40–49 yr	406 (58)	784 (57)	
Education			<0.01
Not a high-school graduate	143 (20)	121 (9)	
High-school graduate	280 (40)	395 (29)	
Attended college or college graduate	277 (39)	860 (62)	
Unknown	2 (<1)	0	
Smoking status			<0.01
Current smoker	358 (51)	419 (30)	
Former smoker	150 (21)	367 (27)	
Never smoked	194 (28)	590 (43)	
History of hypertension	272 (39)	281 (20)	<0.01
Unknown	0	1 (<1)	
History of diabetes	44 (6)	72 (5)	0.37
Unknown	5 (<1)	2 (<1)	
Family history of hemorrhagic stroke	51 (7)	56 (4)	<0.01
Unknown	137 (20)	246 (18)	
Regular alcohol use (>2 drinks/day)	95 (14)	96 (7)	<0.01
Use of cocaine on index day or preceding day	12 (2)	2 (<1)	<0.01
Oral-contraceptive use during the 3-day window interval†	36 (9)	74 (10)	0.88
Body-mass index‡			0.03
<24	233 (33)	391 (28)	
24–30	295 (42)	659 (48)	
>30	169 (24)	322 (23)	
Unknown	5 (<1)	4 (<1)	
Cold or influenza-like symptoms before index day	114 (16)	269 (20)	0.11
Unknown	39 (6)	54 (4)	

*Among the 708 patients who were enrolled, 6 were excluded from the analysis: there were no matched control subjects for 3 patients, 2 patients completed interviews more than 30 days after their stroke, and the index date could not be determined in the case of 1 patient.

†Only women were included in the analysis.

‡Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

TABLE 3. FREQUENCY OF EXPOSURE TO PHARMACOLOGIC AGENTS OTHER THAN PHENYLPROPANOLAMINE DURING THE THREE-DAY WINDOW OF EXPOSURE.

TYPE OF AGENT	PATIENTS (N=702)	CONTROLS (N=1376)	P VALUE
	number (percent)		
Acetylsalicylic acid	79 (11.3)	133 (9.7)	0.29
Nonsteroidal antiinflammatory drugs	114 (16.2)	292 (21.2)	0.01
Dextromethorphan hydrobromide	25 (3.6)	44 (3.2)	0.76
Sympathomimetic agents other than phenylpropanolamine			
Oral preparations*	58 (8.3)	115 (8.4)	0.99
Inhaled preparations	11 (1.6)	32 (2.3)	0.32
Nasal preparations	8 (1.1)	15 (1.1)	0.90
Stimulants or anorectics that did not contain phenylpropanolamine	4 (0.6)	12 (0.9)	0.63
Oral anticoagulants	2 (0.3)	6 (0.4)	0.72
Agents containing caffeine	49 (7.0)	40 (2.9)	<0.01
Agents containing nicotine	9 (1.3)	1 (0.1)	<0.01

*These agents included medications that contained pseudoephedrine hydrochloride, phenylephrine, ephedrine, and epinephrine.

was lower for men than for women (0.62 vs. 1.54), indicating that sex may modify the effect of phenylpropanolamine on the risk of hemorrhagic stroke. We present the results of the analysis of all subjects because it was a prespecified aim. No men were exposed to phenylpropanolamine through the use of an appetite suppressant. With respect to the risk associated with the first use of a product containing phenylpropanolamine, the adjusted odds ratios for men and women were similar (2.95 and 3.13, respectively).

In supplementary analyses, we examined the relation between the recency of exposure to phenylpropanolamine and the risk of hemorrhagic stroke. For these analyses, the definition of current use was consumption within 24 hours before the focal time, and both men and women were included. The adjusted odds ratio associated with current use (1.61; 95 percent confidence interval, 0.83 to 3.10; P=0.16) was slightly higher than that associated with the use of products containing phenylpropanolamine two or three days before the focal time (1.16; 95 percent confidence interval, 0.40 to 3.38; P=0.79). When current use was further stratified according to whether or not it was the first use, the risk was concentrated among first-time users (adjusted odds ratio for first-time use, 3.14; 95 percent confidence interval, 0.96 to 10.28; P=0.06; adjusted odds ratio for use other than first-time use, 1.20; 95 percent confidence interval, 0.54 to 2.67; P=0.66).

We also examined the possibility of a dose effect. Among 21 male and female control subjects with current use of products containing phenylpropanolamine, the median dose of phenylpropanolamine was 75 mg. Analyses showed that the point estimate of the odds ratio was higher for current use involving doses above the median dose of 75 mg (adjusted odds ratio, 2.30; 95 percent confidence interval, 0.96 to 5.54; P=0.06) than for current use involving lower doses (adjusted odds ratio, 1.01; 95 percent confidence interval, 0.36 to 2.80; P=0.98).

To examine the potential effect of ambiguity in the focal time, we recalculated the odds ratios after excluding 154 patients who were classified as having a definite sentinel headache (76 patients) or a possible sentinel headache (78) and their matched controls. The adjusted odds ratios for women were 12.6 (95 percent confidence interval, 1.01 to 157.75; P=0.05) for the use of appetite suppressants containing phenylpropanolamine within three days before the focal time and 3.32 (95 percent confidence interval, 0.72 to 15.2; P=0.12) for the first use. The adjusted odds

TABLE 4. ASSOCIATION BETWEEN THE USE OF PRODUCTS CONTAINING PHENYLPROPANOLAMINE AND THE RISK OF HEMORRHAGIC STROKE.*

VARIABLE	PATIENTS	CONTROLS	ADJUSTED MATCHED ODDS RATIO (95% CI)†	P VALUE
	number (percent)			
Women				
No. in analysis	383	750		
No use of products containing phenylpropanolamine	355 (92.7)	713 (95.1)	—	
Any use of products containing phenylpropanolamine‡	21 (5.5)	20 (2.7)	1.98 (1.00–3.90)	0.05
Cough or cold remedy	16 (4.2)	19 (2.5)	1.54 (0.76–3.14)	0.23
Appetite suppressant	6 (1.6)	1 (0.1)	16.58 (1.51–182.21)	0.02
First use of products containing phenylpropanolamine	7 (1.8)	4 (0.5)	3.13 (0.86–11.46)	0.08
Men				
No. in analysis	319	626		
No use of products containing phenylpropanolamine	309 (96.9)	597 (95.4)	—	
Any use of products containing phenylpropanolamine	6 (1.9)	13 (2.1)	0.62 (0.20–1.92)	0.41
Cough or cold remedy	6 (1.9)	13 (2.1)	0.62 (0.20–1.92)	0.41
Appetite suppressant	0	0	—	
First use of products containing phenylpropanolamine	1 (0.3)	1 (0.2)	2.95 (0.15–59.59)	0.48
All subjects				
No. in analysis	702	1376		
No use of products containing phenylpropanolamine	664 (94.6)	1310 (95.2)	—	
Any use of products containing phenylpropanolamine‡§	27 (3.8)	33 (2.4)	1.49 (0.84–2.64)	0.17
Cough or cold remedy	22 (3.1)	32 (2.3)	1.23 (0.68–2.24)	0.49
Appetite suppressant	6 (0.9)	1 (0.1)	15.92 (1.38–184.13)	0.03
First use of products containing phenylpropanolamine	8 (1.1)	5 (0.4)	3.14 (0.96–10.28)	0.06

*No use of products containing phenylpropanolamine was defined as the absence of the use of these products during the two weeks preceding the index day; 11 patients and 33 controls used such products between two weeks and three days before the index day but were included in the analysis with the use of an additional exposure term. Any use of products containing phenylpropanolamine was defined as use on the index date before the focal time or during the preceding three calendar days. The first use was defined as the use of any product containing phenylpropanolamine within 24 hours before the focal time, with no other uses in the two weeks before the index day. All events that occurred after a first use involved cough or cold remedies. CI denotes confidence interval.

†Odds ratios were adjusted for smoking status, presence or absence of hypertension, race (black vs. nonblack), and level of education.

‡One female patient used both a cough or cold remedy and an appetite suppressant that contained phenylpropanolamine during the window of exposure.

§Of the 27 patients who were exposed, 18 had a subarachnoid hemorrhage and 9 had an intraparenchymal hemorrhage.

ratios for men and women combined were 1.33 for any use of a product containing phenylpropanolamine within three days before the focal time (95 percent confidence interval, 0.70 to 2.55; P=0.39), 1.12 for the use of cough or cold remedies containing phenylpropanolamine (95 percent confidence interval, 0.57 to 2.20; P=0.74), 12.10 for the use of appetite suppressants containing phenylpropanolamine (95 percent confidence interval, 0.92 to 159.14; P=0.06), and 3.34 for the first use of a product containing phenylpropanolamine (95 percent confidence interval, 0.87 to 12.87; P=0.08).

DISCUSSION

Among women between the ages of 18 and 49 years, the use of a product containing phenylpropanolamine as an appetite suppressant was associated with an increased risk of hemorrhagic stroke. There was also a suggestion of an association in women with any first use of phenylpropanolamine, which involved only cough or cold remedies. No significantly increased risk of hemorrhagic stroke was observed among men who used a cough or cold remedy that contained phenylpropanolamine. Because no male subject reported the use of appetite suppressants con-

taining phenylpropanolamine and only two reported the first use of a product containing phenylpropanolamine, we could not determine whether men are at increased risk for hemorrhagic stroke under these conditions.

Before our study, published information concerning the association between the use of phenylpropanolamine and the risk of hemorrhagic stroke came from one epidemiologic study[19] and several case reports.[1] The epidemiologic study found no association, but design limitations reduced its contribution to the assessment of the safety of phenylpropanolamine. Although the case reports called attention to a possible association between the use of phenylpropanolamine and the risk of hemorrhagic stroke, the absence of control subjects meant that these studies could not produce evidence that meets the usual criteria for valid scientific inference. Our study provides strong epidemiologic evidence of the association between the use of phenylpropanolamine and the risk of hemorrhagic stroke.

Other than a valid association between the use of phenylpropanolamine and the risk of stroke, possible explanations for our findings include chance, residual confounding, and other forms of bias. Regarding chance, the lower bound of the 95 percent confidence interval is greater than 1 for the odds ratio pertaining to the use of products containing phenylpropanolamine as an appetite suppressant among women. The lower bound falls at or just below 1 for odds ratios pertaining to any use of products containing phenylpropanolamine among women (not a prespecified research aim) and the first use among women. Although these two odds ratios are not statistically significant by conventional criteria (95 percent confidence interval excluding 1), their associated probabilities are sufficiently low to arouse concern regarding safety.

Residual confounding refers to incomplete adjustment for factors related to both exposure and outcome. Although there may have been residual confounding in the Hemorrhagic Stroke Project, our data provide little support for the presumption that it significantly distorted the observed association between phenylpropanolamine and hemorrhagic stroke. In particular, adjustment for known potential confounders did not produce odds ratios that were markedly different from the unadjusted figures. As in any research study, however, it is possible that unmeasured confounders contributed to the observed association between phenylpropanolamine and hemorrhagic stroke.

Biases that might have affected our study include temporal-precedence bias, recall bias, and selection bias. Temporal-precedence bias refers to a systematic error in which an exposure is counted although the exposure occurs after the onset of the disease under study, often in response to disease symptoms.[20] We checked for temporal-precedence bias with specific analytic strategies for patients with sentinel headache and found no evidence that it distorted the main findings.

Recall bias refers to the tendency of case subjects, as compared with control subjects, to have more or less accurate recall of exposures. Because of the potential importance of recall bias, we used several safeguards, including a highly structured interview and the blinding of subjects to the study's phenylpropanolamine hypothesis. In addition, to overcome greater stimulation for recall among patients, we used a shorter interval between the focal time and interview dates for control subjects.

Selection bias refers to the preferential referral to a case–control study of patients or control subjects with (or without) the exposure under study.[21] Publicity about phenylpropanolamine and stroke might have led physicians to preferentially seek a diagnosis of hemorrhage or to refer a patient to our study if there had been a history of phenylpropanolamine use.[22] Although case–control studies cannot assuredly avoid such biases, we adopted several strategies to reduce the possibility of bias in the selection of patients, including active case surveillance and objective determination of eligibility.

Several features of the Hemorrhagic Stroke Project provide evidence of the validity of the associations found between the use of phenylpropanolamine and the risk of hemorrhagic stroke. First, uniform procedures to determine the eligibility of the subjects minimized bias in enrollment. Second, extensive procedures for ascertaining and verifying exposure to phenylpropanolamine were successfully implemented to reduce error and bias in exposure classification. Third, the odds ratios for the prespecified study aims regarding the use of appetite suppressants in women (16.58) and first use (3.13) were large. Fourth, the data suggest an association with hemorrhagic stroke for the two major formulations of phenylpropanolamine (i.e., cough or cold remedy and appetite suppressant).

Although data from the Hemorrhagic Stroke Project cannot be used to estimate individual risk, they can be used to estimate the number of people who must be exposed to phenylpropanolamine in order to observe one occurrence of hemorrhagic stroke (number needed to harm). Using a daily incidence rate of hemorrhagic stroke of 0.6 per million for persons 35 to 54 years of age[23] and assuming a range of odds ratios from 1.51 to 16.58, we estimate that 1 woman may have a stroke due to phenylpropanolamine for every 107,000 to 3,268,000 women who use products containing phenylpropanolamine as an appetite suppressant within a three-day window.

In conclusion, the results of the Hemorrhagic Stroke Project suggest that phenylpropanolamine in appetite suppressants, and possibly also as a cold and cough remedy, is an independent risk factor for hem-

orrhagic stroke in women. For both persons considering the use of phenylpropanolamine and for policy makers, our study provides important data for a contemporary assessment of risks associated with the use of this common medication.

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APPENDIX

The following regional centers, hospitals, coordinators, and institutional investigators participated in the Hemorrhagic Stroke Project: *Clinical centers:* University of Cincinnati (17 hospitals, 233 patients; principal investigators: J.P. Broderick, T. Brott; study coordinators: L. Sauerbeck, J. Carrozzella) — Bethesda North Hospital, Bethesda Oak Hospital, Clermont Mercy Hospital, Deaconess Hospital, Good Samaritan Hospital, Mercy Hospital (Anderson), Mercy Hospital (Fairfield), Mercy Franciscan Hospital (Western Hills), Mercy Franciscan Hospital (Mount Airy), Saint Elizabeth Medical Center (South), Saint Elizabeth Medical Center (North), Saint Luke Hospital (West), Saint Luke Hospital (East), Christ Hospital, Jewish Hospital, University Hospital and Veterans Affairs Medical Center, Cincinnati; University of Texas Medical School (1 hospital, 136 patients; principal investigator: L.B. Morgenstern; study coordinator: M. Cox) — Hermann Hospital: L.B. Morgenstern; and Brown University (2 hospitals, 109 patients; principal investigators: E. Feldmann, J.L. Wilterdink; study coordinators: C. Cirillo, N. Thovmasian) — Miriam Hospital: E. Feldmann; Rhode Island Hospital: E. Feldmann. *Coordinating Center:* Yale University School of Medicine (23 hospitals, 268 patients; principal investigators: L.M. Brass, R.I. Horwitz, W.N. Kernan, C.M. Viscoli; study coordinator: K. Krompf) — Bridgeport Hospital: K.N. Sena; Danbury Hospital: J.M. Murphy; Gaylord Hospital: R. Stein; Greenwich Hospital: W.A. Camp; Griffin Hospital: J.B. Butler; Hartford Hospital: R.H. Simon; Hospital for Special Care: S. Yoon-DeLuca; Hospital of Saint Raphael: P.S. Dickey; Lawrence and Memorial Hospital: L.I. Radin; Manchester Memorial Hospital: R.H. Berland; Middlesex Hospital: K.J. Kiwak; New Britain General Hospital: B.G. Spass; Norwalk Hospital: R.A. Levine; Rehabilitation Hospital of Connecticut: D. Feingold; Saint Francis Hospital and Medical Center (Saint Francis Campus): P.B. Wade; Saint Francis Hospital and Medical Center (Mount Sinai Campus): G.H. Belt; Saint Joseph Medical Center: E.D. Xistris; Saint Mary's Hospital: K.A. Kaplove; Saint Vincent's Medical Center: P. Shear; Stamford Hospital: M.H. Camel; Waterbury Hospital: J.O. Bizzozero; William W. Backus Hospital: C. Salame; and Yale–New Haven Hospital: R.I. Horwitz. *Scientific Advisory Group:* L.C. Lasagna (chair), S. Suissa, and J.P. Mohr.

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