2005N–0374
Use of Ozone-Depleting Substances: Essential-Use Determination of Over-the-Counter (OTC) Epinephrine Metered Dose Inhalers

Submitted to the Nonprescirption Drugs and Pulmonary-Allergy Drugs Advisory Committees

Wyeth Consumer Healthcare
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EPINEPHRINE OTC AC BRIEFING DOC

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I. INTRODUCTION

On November 29, 2005, FDA announced that a joint meeting of the Non-Prescription Drugs and Pulmonary and Allergy Advisory Committees would be held on January 24, 2006, to discuss the essential use status of epinephrine, an Over-The-Counter (OTC) drug delivered by metered-dose inhalers (MDI) that use CFCs as the propellant.

Wyeth Consumer Healthcare is an interested party to these proceedings in that we market Primatene Mist, an MDI containing epinephrine that uses CFC-12 and CFC-114 as propellants. Primatene Mist is an Over-The-Counter (OTC) product indicated for the temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath. Primatene represents 84% of the OTC MDI epinephrine market; there are no other OTC asthma rescue products.

Epinephrine MDI is a product that consumers have relied upon for more than 40 years. While standards have evolved since the first approval of an epinephrine MDI, there is data from the extensive market history along with more limited study data which provides more than adequate information to support the safety and efficacy of this product. We also have information from a variety of sources indicating that epinephrine MDIs meet all three elements of essential use as defined in 21 CFR 2.125(f), specifically that:

> (i) Substantial technical barriers exist to formulating the product without Ozone Depleting Substances (ODSs);
>
> (ii) The product provides an unavailable important public health benefit; and
>
> (iii) Use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

Each of these elements is important to the overall consideration of essential use.

Epinephrine should retain its essential use designation for use as an OTC metered dose inhaler to relieve the symptoms of asthma. In this document, Wyeth Consumer Healthcare will demonstrate that epinephrine OTC MDI satisfies all three essential use criteria.

Wyeth respects the importance of phasing out of ODS, while recognizing that epinephrine OTC provides a unique and substantial health benefit which will go unfulfilled if the essential use designation is not granted. Therefore, Wyeth proposes epinephrine OTC should remain available until an HFA-containing replacement product is available.

II. CFC RELEASE IS SMALL AND JUSTIFIED

In 1987 the United States, as a Party to the Montreal Protocol on Substances that Deplete the Ozone Layer, agreed to phase out production and importation of ODSs, including CFCs. The schedule in the Montreal Protocol calls for production and consumption of CFCs in developed countries to be reduced 75% by 1994 with complete phase-out by 1996, and in developing countries to be reduced 50% by 2005, 85% by 2007 with complete phase-out by 2010.

According to the Montreal Protocol, an exception to the complete phase-out is allowable "to the extent that the parties decide to permit the level of production or consumption that is necessary to satisfy uses agreed by them to be essential." In the United States, under the Clean Air Act, the Food and Drug Administration (FDA), in consultation with the Environmental Protection Agency (EPA), is required to determine whether the use of an ODS in an FDA-regulated product is essential. FDA lists essential medical products in 21 CFR 2.125(e). Metered-dose epinephrine for oral inhalation is currently listed as a human drug in which the use of ODSs is essential.

The United States has agreed to phase-out eventually all uses of CFCs. FDA has stated that it will ensure the health and safety of patients in the United States during the transition away from CFC use in medical products. The criteria for this transition are established in 21 CFR 2.125. Every year, US companies who wish to use CFCs must file a justification with the EPA explaining how much they want to use, what they will be using them for, and the basis for their essentiality. In the case of medical products, EPA then consults with FDA to confirm that there is an essential need for the CFCs requested, and to determine how the available CFCs should be allocated.

For the year 2005, the US Environmental Protection Agency granted to Wyeth Consumer Healthcare (WCH) an essential use allowance of 73.40 metric tons of CFC-11, CFC-12

and/or CFC-114 for the production of its epinephrine metered-dose inhalers (MDI). Wyeth expects to apply for similar annual allowances while producing this product.

Numerous organizations have provided estimates of total annual CFC emission rates. Among the most widely cited are the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS) and the Intergovernmental Panel on Climate Change (IPCC). Of the two sources, the IPCC is more comprehensive.

According to the IPCC report, global releases of CFC-11 and CFC-12 in 2002 were estimated at 70-90,000 and 110-130,000 metric tons, respectively. Releases of total "major" CFC in that year were estimated at 185-232,000 metric tons. Since CFC-11 and CFC-12 represented over 90% of the total CFC releases, releases of other CFC's such as CFC-114 are not estimated in the report.

Table 1. CFC Emissions Estimates from the UN Environment Programme

CFC	**2002 Estimate (metric tons/yr)**	**Trend (% of concentration)**	**2005 Projected (based on trend)**
CFC-11	70,000-90,000	-0.7-1.1	68,000-89,000
CFC-12	110,000-130,000	+0.04-+0.16	110,000-130,000
Total "major" CFC	185,000-232,000		178,000-219,000 (100%)
Wyeth CFC-12 Contribution			**73.4 (0.04%)**

As noted in Table 1, CFC releases decrease slightly or, in the case of CFC-12, increase slightly each year which, according to the report's authors, is due to "substantial banks of this material built up from past production." Therefore, 2005 release estimates are not expected to differ substantially from those in 2002.

Using these figures, if all of WCH's allowance of 73.4 metric tons were released in 2005, this release would represent a maximum of 0.04% of both total CFC emissions and combined emissions of CFC-11 and CFC-12 for that year.

III. THERE ARE NO TECHNICALLY FEASIBLE ALTERNATIVES AT THIS TIME

Providing an alternative to a CFC propellant is a complex process. There are two stages to the development of an HFA alternative: First, there is the challenge of developing an appropriate formulation that delivers the appropriate amount of medication to the appropriate part of the lung. Only after those criteria are met can the company move to the

second phase of development, which is clinical testing to prove that the product is equivalent to the existing CFC product.

Wyeth's goal is to develop a satisfactory alternative propellant to CFC, and for years we have been investigating different ways to achieve this goal. A brief summary of our progress is as follows:

A. Internal Reformulation Alternatives Unsuccessful to Date

For many years, Wyeth conducted a reformulation program to replace CFCs with an HFA propellant. Several prototypes were successful with respect to ingredient compatibility, preliminary stability, and spray pattern. However, the prototypes were unacceptable with respect to organoleptic properties; the higher pressure and higher alcohol content produced unacceptable sensations for the user. Additionally, there was concern that the high alcohol content could exacerbate asthma symptoms. For these reasons efforts with these prototypes were abandoned, and different types of alternatives were pursued.

B. Multiple Attempts to Access HFA Alternatives

Since Wyeth was not successful with an HFA reformulation, we looked to alternative active ingredients that could be sold on an OTC basis. This included evaluations of pirbuterol, albuterol tablets, HFA albuterol MDI, and epinephrine dry powder inhaler. For a variety of reasons, none of these projects were viable alternatives. For example, Wyeth conducted clinical trials with albuterol tablets to evaluate their potential as an OTC alternative to the CFC MDI. The time to onset of action was not rapid enough to qualify it as an acceptable replacement for an OTC epinephrine MDI, and the program was not progressed past the initial clinical trials.

C. Partnership to Reformulate to HFA

Wyeth identified a partner to manufacture our OTC epinephrine MDI, Armstrong Pharmaceuticals. Armstrong has demonstrated formulation expertise, and Wyeth is now partnering with them to continue development of an HFA epinephrine MDI. Armstrong initiated their reformulation program several years ago, and it is anticipated the clinical program and FDA filing, will be completed in 2011.

IV. OTC EPINEPHRINE MDI PROVIDES SUBSTANTIAL PUBLIC HEALTH BENEFITS

A. Clinical Benefits

1. Epinephrine MDI Has a Long History of Safe and Effective OTC Use

OTC epinephrine MDI has a long history of safe and effective use in the United States. The first OTC epinephrine MDI was approved in 1956 (NDA 10-374) for the temporary relief of asthma symptoms. Wyeth began marketing that product under the Primatene Mist name in 1964, and received approval for its own NDA (16-126) in 1967. Through its marketing history we estimate that 130 million units have been sold and approximately 6 million Americans currently rely in this product, either in addition to their existing asthma prescription medication or, to a lesser extent, as their sole asthma relief product. Epinephrine MDI is indicated for the temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath, and importantly it is the only asthma inhaler available OTC.

2. Epinephrine MDI is Consistent with NAEPP Guidelines for Mild Intermittent Asthma

In 1991, the National Heart, Lung and Blood Institute published treatment guidelines for asthma under its National Asthma Education and Prevention Program (NAEPP). These have been updated on a regular basis, the most recent being in 2002 (Appendix 2). Under these guidelines, asthmatics were categorized in four classes of severity, viz., mild intermittent, mild persistent, moderate persistent and severe persistent. It is recommended that mild intermittent asthmatics do not need regular daily medication. All other asthmatics are required to take some form of daily medication. It is recommended that all asthmatics use an inhaled short-acting beta-agonist for relief of symptoms when needed.

The indication for epinephrine OTC in the above section is consistent with NAEPP category of mild intermittent asthma, and is consistent with the recommendation for quick relief that specifies a short-acting bronchodilator. Although it is not mentioned specifically in the guidelines, epinephrine MDI is an effective short acting bronchodilator labeled for use in accordance with these guidelines, and is the only short-acting bronchodilator available without a prescription.

a. Pharmacology: Epinephrine is Short Acting

Epinephrine has a long history of use in acute asthma. Epinephrine is a non-selective beta-agonist with alpha-agonist activity. It has been used subcutaneously as well as by inhalation. Hallmarks of epinephrine's activity are its rapid onset, and short duration of action. The table below compares epinephrine to albuterol, a selective beta-agonist commonly used to treat the symptoms of asthma.

Table 2. Comparative Pharmacology of Nebulized Albuterol and Epinephrine

Sympathomimetic	Adrenergic receptor activity	Onse of actiont (min)	Duration of action (hours)
Albuterol	$ß_1 < ß_2$	Inh[a]: within 5	3-6
Epinephrine	$\alpha, ß_1, ß_2$	sc: 5-10	4-6
		Inh[a]: 1-5	1-3

a: administered via aerosol, bulb nebulizer or IPPB

(Source: online.factsandcomparisons.com)

Epinephrine delivered by a metered dose inhaler has been shown to have a very rapid onset of action with a short duration, making it ideal for rescue (see table below).

Table 3. Pharmacology of Epinephrine MDI

Sympathomimetic	Adrenergic receptor activity	Onset of action	Duration of action
epinephrine	$\alpha, ß_1, ß_2$	Inh: 15 seconds	23 min

(Source: Dauphinee, 1994)

b. Efficacy of Epinephrine MDI

In a randomized, double-blind, placebo controlled, two-way crossover study in subjects with mild-to-moderate asthma, 11/24 (46%) subjects receiving a single inhalation of epinephrine (160 mcg epinephrine base) showed a clinically significant improvement in FEV1 (defined *a priori* as >15% improvement) compared to 1/23 (4%) receiving placebo. A second inhalation was administered 1 minute after the first inhalation. After receiving 2 inhalations, 21/24 subjects (88%) receiving epinephrine showed meaningful improvement compared to 4/23 (16%) receiving placebo. The time to peak response for epinephrine was 7.6 minutes (range 0.75- 30 minutes) and the duration of response was 23 minutes (range 5-30 minutes). (Dauphinee, 1994).

A second study commissioned by Wyeth was conducted to evaluate the safety and efficacy of inhaled and oral OTC bronchodilators in moderate-to-severe asthmatics. In that randomized, double blind, placebo controlled, crossover study, subjects received 2 inhalations of epinephrine (200mcg/inhalation) one minute apart followed by either an oral combination of bronchodilators or an inhaled selective beta inhaler, 15 minutes later. With respect to the effects of inhaled epinephrine, in all 12 subjects, FEV1 increased 15% over baseline within 15 seconds of the second inhalation of epinephrine. (Pinnas et al., 1991)

c. Safety of Epinephrine MDI

i. Supra-therapeutic doses administered by MDI

Primatene Mist delivers 220 mcg of epinephrine per inhalation. The recommended dosing regimen of Primatene is one inhalation followed by another inhalation given a minute later. Hence the maximum recommended dose per asthma attack is 440 mcg of epinephrine. The following two studies examined the effects of 3 to 10 fold higher epinephrine doses administered by MDI.

A study conducted by Warren (Warren, 1986) examined the systemic absorption of epinephrine by MDI (competitive product; not Primatene Mist) and by subcutaneous injection (SC). Six healthy volunteers received either MDI or SC epinephrine in randomized order. The doses administered were 2400 mcg (15 actuations) and 4800 mcg (30 actuations) by MDI or 300 mcg by SC injection. Their results were as follows:

Table 4. Systemic Absorption of Epinephrine MDI vs Subcutaneous Administration

Treatment	Cmax	Tmax	Increase in pulse rate above baseline
SC epinephrine 300mcg	2.43 nmol/L	10 minutes	7 bpm
Inhaled 2400 mcg	1.50	1 minute	9 bpm
Inhaled 4800 mcg	4.22	1 minute	

The key findings of this study were that inhaled epinephrine, even at supratherapeutic doses, was rapidly absorbed and rapidly cleared from the systemic circulation. Plasma epinephrine levels and physiologic finger tremor (a measure of beta-2 activity) returned to baseline 20 minutes after the administration of even the highest inhaled doses. In contrast, epinephrine blood concentrations remained elevated for 40 minutes after subcutaneous epinephrine

administration. Both routes of administration resulted in small increases in pulse rate which were short lived. Furthermore, relative bioavailability showed that only about 5% of the inhaled dose was absorbed compared to 100% of the subcutaneous dose.

Heilborn conducted a similar study in 25 healthy volunteers. Volunteers received either 500mcg SC epinephrine or 1500 mcg (10 actuations) or 3000 mcg (20 actuations) of MDI epinephrine (competitive product; not Primatene Mist) (Heilborn, 1986).

Table 5. Comparison of Three Doses of Epinephrine

Treatment	Cmax	Tmax	Reported side effects
SC epinephrine 500mcg (N=8)	4.65 $\pm$ 1.09 nmol/L	15-120 minutes	Tremor (3) Palpitations (2)
Inhaled 1500 mcg (N=6)	2.72 $\pm$ 0.84 nmol/L	Within 5 minutes	None
Inhaled 3000 mcg (N=8)	7.19 $\pm$ 1.78 nmol/L	Within 20 minutes	Nausea (4)

The conclusion of this study was that inhaled epinephrine, also at higher doses than that recommended for asthma, was well tolerated following rapid absorption.

ii. Fatalities and Serious Adverse Events reported to Wyeth:

In September 2005, Wyeth conducted a review of Primatene associated fatalities reported to the company since 1964 (Appendix 3). The initial serious case was reported to Whitehall Robins in 1990. The initial fatality case was received in 1992. In October 2005, this data was again searched to include all SAEs reported to the Wyeth, (Appendix 4).

During this period, we have received reports of 106 reports containing 229 serious adverse events coincident with the use of Primatene Mist (including 33 fatalities and a total of 229 SAEs).

It should be noted that, due to time constraints, these data reflect only what is available in Wyeth's files and do not account for data reported directly to the FDA through the MedWatch program. The electronic records AE records available through Freedom of Information do not contain narrative information (to assess causality). Since in our experience, requesting MedWatch data through FDA takes approximately six months,

Wyeth was unable to provide these data. Since Wyeth is the primary manufacturer of epinephrine OTC MDI, we feel confident that the majority of the reports contained in the FDA MedWatch files are accounted for in our own files.

(a) Fatalities

A total of 33 fatal cases coincident with the use of Primatene Mist have been reported to Wyeth since 1964. Of the fatal cases, 24 reported by consumers, 8 cases were reported by health care professionals and 1 was published in the medical literature. Of these cases, 19 provided no details or the caller said that they had heard about a fatality. For example, a health care professional called in a case pertaining to the death of a model. This was followed by 8 more reports describing the same case. Similarly, a caller reported that a "pharmacist said product has caused 6 deaths". Relevant information was not provided to ascertain a link between Primatene and death.

Of the remaining cases, there were 14 fatalities. The Table below shows the ascribed causality.

Table 6. Fatalities Coincident with Primatene Mist

Cause of death	Causality
6 asthma	insufficient information= 3, cannot exclude =1, not related =2
1 myocardial infarction	cannot exclude
1 cerebral hemorrhage, cardiac arrest	insufficient information
1 respiratory failure due to Primatene overuse	insufficient information
2 abuse, overuse	intravenous abuse -not related overuse -insufficient information
1 cerebral hemorrhage secondary to chronic hypertension	insufficient information
1 road traffic accident	not related
1 ischemic cardiomyopathy/myocardial infarction	insufficient information

(b) Non-fatal SAEs

As shown in Table 1.0-1 in Appendix 3, we have received reports of 106 reports containing 229 serious adverse events coincident with the use of Primatene Mist. The non-fatal SAEs were distributed among system organ classes without any apparent signal to suggest particular pathology. Since the preparation of this report in October, we have uncovered another literature-reported case involving a 73 year old male who suffered an intracerebral hemorrhage after abuse/overdose of over-the-counter inhaled epinephrine. The brand name of the product was not specified (Cartwright, 2005).

(c) Adverse Events Reported To The American Association Of Poison Control Centers

The American Association of Poison Control Centers (AAPCC) was requested to search their database for all reports associated with the use of inhaled epinephrine for the time period January 1, 1988 to December 31, 2004. (Appendix 5).

For this period, a total of 431 exposures were reported to AAPCC. The results (including cases published by the AAPCC) were as follows:

Table 7. Outcome summary of exposures received by AAPCC

AAPCC designated Outcome	Frequency	Proportion of all exposures (%)
Death	3	0.5
Major Effect	3	0.5
Moderate Effect	41	9.5
Minor Effect	109	25.3
No Effect	94	21.8
Not Followed, judged as nontoxic exposure (clinical effects not expected)	22	5.1
Not Followed, minimal clinical effects possible (no more than minor effect possible	95	22.0
Unable to follow, judged as a potentially toxic exposure	34	7.9
Unrelated effect, the exposure was probably not responsible for the effect(s)	32	7.4

Major Effect: The patient exhibited signs or symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

Moderate Effect: the patient exhibited signs or symptoms as a result of the exposure which were more pronounced, more prolonged, or more of a systematic nature than minor symptoms.

Minor Effect: The patient exhibited some signs or symptoms as a result of the exposure, but they were minimally bothersome to the patient.

These data, similarly to those reported to WCH, attest to the safety of Primatene Mist.

iii. Conclusion

From 1964 to October, 2005, we estimate that 130 million units of Primatene Mist were purchased by consumers. Given the extensive usage of the product and the background incidence of cardiac and asthma deaths, the preceding data consisting of 36 fatalities and a total of 229 SAEs did not reveal a signal for death or any other SAEs associated with epinephrine products.

3. Published Literature

A comprehensive literature search was performed in the following databases:

Medline®; Biosis Previews®, EMBASE, SciSearch®, Int. Pharm. Abstracts, Derwent Drug File without restriction to year. The search terms included Epinephrine (aerosols, Inhalation, Nebulizer, Vaporizer, Metered Dose Inhalers, Spray, Mist) and Asthma. The search results returned a total of twenty-one (21) clinical trials. These were broken down by route of

administration as follows: metered-dose inhalers (n=4), nebulizer (n=6), subcutaneous injection (n=4). In addition seven clinical trials included the use of epinephrine for acute bronchiolitis which may represent a clinical model symptomatically similar to acute asthma.

The 14 clinical trials of epinephrine in asthma indicate that this drug is effective in the management of this condition and that the preferred route of administration is via inhalation which reduces the incidence of side effects. Summaries of these trials can be found in Appendix 6.

4. Regulatory History of OTC Epinephrine

During the last 49 years of product availability, the FDA and its Advisory Committees have reviewed the safety and efficacy of OTC epinephrine on four separate occasions. Some highlights from those reviews are as follows:

a. 1976 OTC Review

FDA initiated review of all OTC drug products in 1972. Consequently, the use of epinephrine to treat the symptoms of asthma was reviewed by an expert FDA panel, and their assessment was published in 1976. The Panel commented that the response of mild or moderate asthma to epinephrine was quick and there was effective relief. The product was considered safe for OTC use when taken as directed. Additionally, it was stated that "*asthma is a very common disease and it is reasonable to have bronchodilators available without a prescription to avoid any delays associated with obtaining a prescription"* (41 FR 38320).

b. 1986 Final Rule for OTC Bronchodilators

In this Final Rule, the FDA commented that *"Bronchodilator drug products have been available OTC and used extensively for many years. The Agency concludes that the benefits of the continued OTC availability of these drug products outweigh the risks mentioned by the comments. OTC availability of bronchodilator drug products provides asthmatics ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room."*

c. 1994 Advisory Committee

In November 1994 Joint Advisory Committee Meeting of the Pulmonary-Allergy and Nonprescription Drug Advisory Committees considered the status of OTC CFC MDI

epinephrine based on a thorough review of efficacy, safety, and use data. Based on this review, they raised and discussed several points that are still relevant to the OTC status of inhaled epinephrine. Relevant statements from the Committee members and FDA follow.

Dr. Reidenberg felt that there is a population of users adequately served by the OTC product:

> *"…So I think that people have defined a population of patients for whom over-the-counter epinephrine by inhalation seems to be beneficial. They think it is. It relieves the symptoms, and there isn't any evidence that taking it away is going to improve the care of these particular people."*

Dr. Johnson offered the observation:

> *"…I think there is a population of people, not patients, for whom something like the inhalation epinephrine is quite appropriate, who have intermittent wheezing once, twice, three times a year that can be managed with something like this, by self-treatment."*

In response to the assertion that the safety data did not demonstrate that epinephrine was not safe, Dr. Wenzel expressed the opinion:

> *"…there has been very, very little data that has been presented that clearly has told me, anyway, that epinephrine is doing detrimental things to our asthmatic population, or at least to the majority of the "mild asthmatics"…*

While there was no vote and no consensus statement, the overall sentiment was that there continued to be a role for OTC inhaled epinephrine in treating mild, intermittent asthma.

These statements from the experts quoted above, as well as others expressed at the meeting, have been confirmed by consumer research conducted by Wyeth Consumer Healthcare, and by our experience with direct consumer contact. Wyeth has compiled demographic, marketing, and consumer contact information that helps establish a public health benefit for the product, as part of compelling evidence for the continued OTC availability of inhaled epinephrine.

d. July 2005 Proposed Amendment for Bronchodilator Monograph

This Amendment was in response to the 1995 proposal to remove ephedrine products from the Monograph, as not being generally recognized as safe and effective for OTC use. FDA rejected that proposal and reiterated there is a role for OTC bronchodilators for treatment of

the symptoms of asthma. The labeling for OTC bronchodilators was updated to provide for safer and more effective use.

> *"After considering the comments submitted for the 1995 proposal to remove ephedrine and other active ingredients from the FM, FDA is withdrawing that proposal. ... FDA has given serious consideration to the various arguments presented by the comments on the 1995 proposal, has considered other information, and has determined that ephedrine and other bronchodilator ingredients should remain in the FM for self-treatment of mild bronchial asthma for several reasons:*
>
> *" There are people with diagnosed mild bronchial asthma for whom the benefits of symptomatic treatment with OTC bronchodilators for temporary wheezing, shortness of breath, and tightness of chest outweigh the risks of use…*
>
> *"…The[1994 Pulmonary Advisory Committee] Panel noted that wide use of epinephrine aerosols for temporary relief of milder forms of asthma has been attended by few and mild side effects. …The Panel concluded that epinephrine is a safe and effective OTC bronchodilator ingredient when used according to recommended labeling, and FDA included epinephrine in the FM (51 FR 35326 at 35332 through 35333).*

Wyeth agrees with the FDA's and the Advisory Committee's characterization that OTC use of inhaled epinephrine is essential, and supports its continuing the exemption.

e. OTC Labeling

The labeling for OTC epinephrine MDI has been reviewed several times. In July 2005, the FDA revised the safety information for the label. Wyeth is currently in the process of incorporating those changes into the production of Primatene Mist.

The labeling for Primatene Mist consists of several components: the carton, container label, and the package insert. Each of these components provides consumers with the information necessary to make an informed decision on whether the use of the product is right for them. The carton and insert bear full Drug Facts labeling in compliance with the monograph for OTC bronchodilators, and give the following instructions specific to asthma:

Uses

■ for temporary relief of occasional symptoms of mild asthma:
■ wheezing ■ tightness of chest ■ shortness of breath

Warnings

Asthma alert: Because asthma can be life threatening, see a doctor if you

■ are not better in 20 minutes
■ get worse
■ need 12 inhalations in any day
■ use more than 9 inhalations a day for more than 3 days a week
■ have more than 2 asthma attacks in a week

Do not use

■ unless a doctor said you have asthma

Ask a doctor before use if you have

■ ever been hospitalized for asthma

In addition to the full Drug Facts labeling, the Package Insert also bears pictorial instructions regarding the appropriate use of the actuator.

While Wyeth does not actively promote Primatene Mist, it does maintain a website (www.primatene.com) which provides consumers with all the information described above, plus general information about management of asthma.

The current labeling and screenprints of the website are presented in Appendix 7.

B. The Public Benefit of OTC Epinephrine

1. Introduction

This section presents consumer survey data collected over the past ten years through different sources and methodologies. The data is derived from the following sources:

- Research Sponsored by Wyeth
  - 2005 Internet Survey –internet survey of 330 asthmatics, with an augment of 100 OTC-only users. (Data on file)
  - 1999 Survey –telephone survey of approximately 321 asthma sufferers. (Data on file)

- 1994 Market Analysis –a compilation of four independent market research studies (National Family Opinion Research, ICR Survey Group, and two Nielsen studies) selected for developing the profile of non-prescription epinephrine mist and ephedrine combination tablet users from the period November 1993 to August 1994. (Data on file)

- Independent Academic Publications

  - Dickinson BD, Altman RD, Deitchman SD, Champion HC. Safety of over-the-counter inhalers for asthma: report of the council on scientific affairs. Chest 2000; 118(2):522-526.

  - Kuschner WG, Hankinson TC, Wong HH, Blanc PD. Nonprescription bronchodilator medication use in asthma. Chest 1997; 112(4):987-993.

    50 asthmatics were randomly recruited through newspaper advertisements, with an intended recruitment of 50% OTC usage. Demographic information was ascertained, as well as employment and health insurance status and annual household income.

Since the studies were conducted for different purposes, neither the populations surveyed nor the questions asked are identical across all studies. However, each study was conducted according to good market research practices, and the results give us confidence to extrapolate the findings to the US asthmatic population. The data collected in the 2005 Internet Survey is the most current and comprehensive, and will be the primary source for our data in this section.

In this section we will refer to four groups of consumers:

- All Asthmatics – comprised of the US Asthma Population
- Prescription Users – Asthmatics who treat their symptoms only with a prescription product
- Dual Users – Asthmatics who treat their symptoms with both prescription and OTC products

- OTC-Only Users – Asthmatics who treat their symptoms exclusively with an OTC product

2. US Asthmatic Population

In order to understand the unique characteristics of the OTC epinephrine population, it is useful to first understand the characteristics of the adult US asthmatic population.

Asthma is a relatively common disease, and is treated with a variety of medications. According to the CDC, approximately 20.7 million adult Americans suffer from asthma, and 97% of asthma cases are diagnosed by a physician (Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2003, tables 3 and 4, Appendix III table V, data on file). Asthma accounts for 1.7 million emergency room visits, 12.9 million doctor office visits and 500,000 hospitalizations every year.

3. Profile of OTC Epinephrine Consumers

a. Epinephrine OTC Demographics

Consumers who choose to use OTC epinephrine products fall into two categories: Dual users, who use both prescription and OTC products, and OTC-only users, who exclusively use OTC products to manage their asthma symptoms.

The primary similarity between these two groups is that an overwhelming majority of dual and OTC-only consumers had a prior diagnosis of asthma by a health care provider. The 2005 Survey data shows that 92% of OTC-only users and 100% of Dual users have been diagnosed with asthma. These findings are consistent with the data gathered by Kuschner and the 1994 Market Study.

b. Characteristics of Dual Prescription/OTC Treaters

- Previously diagnosed by a physician – as stated above, 100% of the Dual users have been diagnosed with asthma by a physician.

- Dual Users are prone to be under a physician's care. Eighty-eight percent (88%) of Dual Treaters stated that they had seen a physician for their asthma in the previous 12 months (2005 Internet Survey, data on file).

- Physicians are aware their patients use OTC epinephrine. Ninety-two percent (92%) of Dual Users stated that their physician is aware they use OTC epinephrine (2005 Internet Survey data on file)

- OTC Product is Used as a "Stop-Gap"

  When asked "Under what conditions do you use over-the-counter medications?" 36% replied that they use it when they run out of their prescription and another 34% replied they use it when they have an asthma attack and don't have their prescription medication available. Within this same question, 46% responded they use it "when I feel an OTC medication will work better". The meaning behind this is unclear, except to say that these consumers appear to be satisfied with the relief they get from the OTC epinephrine product. (2005 Internet Survey, data on file)

c. Profile of the OTC-Only Treater

- The majority have been diagnosed by a physician – 92% of consumers who exclusively use OTC products to treat their asthma symptoms have been previously diagnosed by a physician. (2005 Internet Survey, data on file)

- Data suggest that the OTC-Only group have more mild asthma than their Dual or Prescription counterparts. As Table 8 below shows, the OTC-Only group had fewer attacks in a three-month period, fewer visits to the Emergency Department and fewer visits to a physician than their Dual Use counterparts. (2005 Internet Survey, data on file)

Table 8. Percent of Asthmatics Seeking Asthma Treatment

	OTC-Only	Dual User	Prescription Only
Mean attacks in three months	3.74	5.39	4.38
Visited doctor in past year for asthma	28%	88%	78%
Been to ER in last year for asthma	9%	36%	21%

Source – 2005 Internet Survey (Data on file)

- Majority of OTC-Only treaters use OTC epinephrine for "rescue" treatment only. Ninety-one percent reported that they use OTC epinephrine only when they are having an asthma attack. (2005 Internet Survey)

- OTC-Only treaters are less likely than average to have medical or prescription drug insurance. Two studies specifically asked respondents about their health care coverage. Wyeth conducted one study, and the data from Kuschner et al are from a published study. The results are summarized in Table 9:

Table 9. OTC-Only Treaters Are Less Likely to Have Medical or Prescription Insurance

	OTC-Only Users		Dual OTC/Rx Users		Rx Only		National Average
	Wyeth Internet Survey 2005	Kuschner, et al., 1997	Wyeth Internet Survey 2005	Kuschner, et al., 1997	Wyeth Internet Survey 2005	Kuschner, et al., 1997	CDC 2005, Kaiser Permanente, 1996
Do not have medical insurance	31%	40%	13%	64%	13%	33%	20%
Do not have prescription plan	38%	--	14%	--	18%	--	23%

4. How Many Consumers Use OTC Products?

Market data show that approximately 5 million canisters of epinephrine OTC were sold in 2004. In the 2005 Internet survey of 330 asthmatics, 29.7% report the use of an OTC medication as part of their asthma treatment, and 10% use an OTC medication as their sole asthma treatment (Wyeth Consumer Healthcare, 2005). This is relatively consistent with the results of the 1999 Survey which reported 10% of asthma sufferers using both an OTC and a prescription, and 5% using OTC medication exclusively, and with the 1994 Nielsen Household Panel which found 12% of asthmatics were Dual users and 9% using OTC exclusively. The study by Kuschner et al., (1997) with a smaller sample size (50) found that 26% (13 subjects) used an OTC medication as part of their asthma treatment. In that study, 30% (15 subjects) reported the exclusive use of OTC medication.

Applying these data to the general adult asthma population, we estimate that approximately between 3 and 6 million consumers use an OTC asthma medication either exclusively or in combination with prescription therapy (Table 10).

Table 10. Asthma Sufferers by Types of Medication used

Type of medication	Asthmatics (in millions)	% of Total
Total	20.7	--
Prescription Only	13.9-16.7	67%-81%
Prescription and OTC	2.0-3.9	10%-19%
OTC-only	1.0-2.0	5%-10%
Other	0.6	3%

Sources: 2005 Internet Survey, CDC Statistics, 2005 (data on file)

5. Why Do Consumers Choose OTC Asthma Medication?

For those consumers who use both a prescription and OTC product, the most common reason for consumers to use an OTC medication is access: to fill a gap when prescription medication has run out or the prescription medication is not readily available. This differs only slightly from the user who uses an OTC only. In the 2005 Internet survey, 50% of the OTC-only consumers stated "It's easier and quicker to obtain", followed by 41% responding "more reasonably priced" as the reason for taking the OTC medication. These statements reinforce the key characteristic of the Primatene user – relatively lower access to healthcare coverage. The lack of healthcare insurance coverage and lack of access to a prescription drug program is one of the leading reasons the OTC consumer continues to rely on OTC epinephrine.

C. Public Health Benefit - Conclusion

These data show that a minority of asthmatics use OTC epinephrine. Of those who do, the majority are physician-diagnosed and the pattern of use suggests that the majority of patients suffer from mild, intermittent asthma. They have a variety of reasons for choosing to use OTC products for their asthma symptoms; some use it because it fills an immediate, unexpected need; others use it because they do not have access to healthcare and it adequately treats their symptoms at a reasonable price. Regardless of their reason for choosing an OTC epinephrine product, consumers are using the products safely, as demonstrated by the adverse event data and the literature.

V. CONCLUSIONS AND RECOMMENDATIONS

As discussed throughout this briefing document, epinephrine MDI meets all three elements of essential use. We have shown that the release of CFCs is small, and justified given the benefit of the product to consumers, and that there is no technically feasible alternative to the product.

There is no other "rescue" OTC asthma medication. While we are optimistic that we will successfully reformulate the product, we are at least six years away from realizing that goal.

Epinephrine MDI provides an important public health benefit. It is a safe and effective product which up to 6 million Americans use to fill a gap when prescription medication has run out, prescription medication is not readily available or as their sole accessible asthma relief product. For the portion of consumers who are uninsured or underinsured, this product fills an important need.

Specific to the questions posed in the November 29 Federal Register notice for this meeting, this briefing document has addressed:

- who uses OTC epinephrine MDI - Section IV(B)(3)
- the number of canisters used annually – Section IV(B)(4)
- that there are no other alternatives should this product be removed from the market – Section IV(B)
- from the literature, the value of the product to the users and why they use it – Section IV(A)(3)
- that use of OTC epinephrine MDI is consistent with NAEPP treatment guidelines – Section IV(A)(2); and
- many consumers with asthma do not have ready access to prescription medication through healthcare professionals – Section IV(B)(3)(c)

In conclusion, if the essential use designation for OTC epinephrine MDI remains intact, consumers will have access to OTC metered dose inhalers while Wyeth moves forward with reformulation of the product.

If the decision is made to deny OTC epinephrine essential use status, all OTC MDI will be removed from the market, which would leave 3 to 6 million people without an OTC asthma medication option.

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Letter to the Editor

Cerebrovascular Diseases

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Intracerebral Hemorrhage Associated with Over-the-Counter Inhaled Epinephrine

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Over the past 25 years, many case reports have described intracerebral hemorrhage (ICH) after ingestion of over-the-counter sympathomimetics [1]. Both oral and nasal delivery systems have been associated with ICH, but inhaled over-the-counter sympathomimetics have not previously been associated with stroke [1]. We present a patient who experienced an ICH after using excessive amounts of over-the-counter inhaled epinephrine.

A 73-year-old male presented with the acute onset of confusion and emesis. His past medical history was significant for a carotid endarterectomy and chronic obstructive pulmonary disease. He had no history of hypertension. Initially, his wife reported his only medication was occasional ibuprofen. He did not drink alcohol but did smoke cigarettes daily. On exam, he was tachycardic (110 beats per-minute) and hypertensive (160/81 mm Hg). He had a fluent aphasia, with frequent paraphasic errors and impaired comprehension, naming, and repetition. No definite facial droop, hemiplegia, or reflex asymmetry was noted on the initial exam, but both toes were up going. CT revealed a left thalamic hemorrhage (fig. 1).

Since the stroke was in a typical location for a hypertensive hemorrhage, his blood pressure was monitored carefully. After the initial hypertensive reading in the emergency room, he remained normotensive throughout the rest of the hospitalization. No signs of chronic hypertension, such as left-ventricular hypertrophy or renal insufficiency, were detected on electrocardiogram, transthoracic echocardiogram or blood chemistries. A urine drug screen was negative and coagulation studies were unremarkable. His wife reported that in addition to ibuprofen, he also used over-the-counter inhaled epinephrine for chronic obstructive pulmonary disease (0.22 mg per puff). She said he took this medication daily and it was not unusual for him to use four puffs at a time. The maximum recommended dose is two puffs every 3 h, and it is not to be used on more than 2 days per week. His wife stated that for several days prior to the stroke, as well as the day the stroke occurred, he had been using 'large amounts' of inhaled epinephrine because his dyspnea had worsened. She was unable to accurately quantify how much he was using.

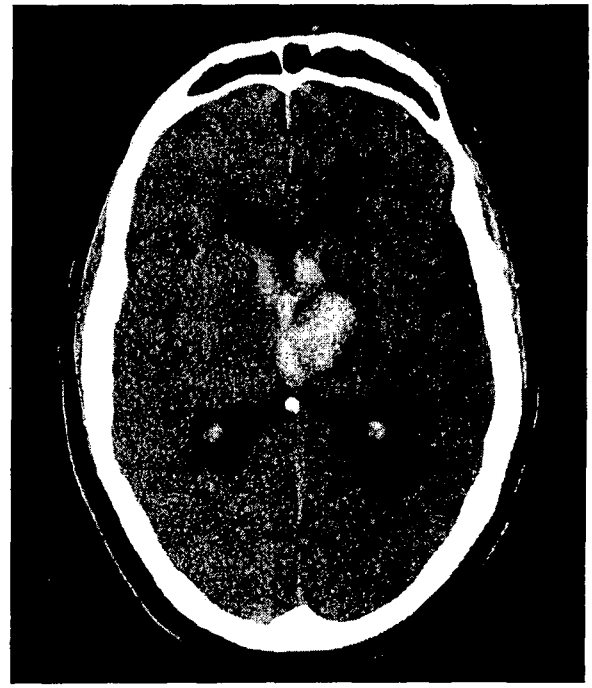

Fig. 1. A non-contrasted CT shows the left thalamic hemorrhage with blood in the third and lateral ventricles.

He improved rapidly after admission. A repeat CT showed no underlying mass. At follow-up 3 months later, he had stopped using inhaled epinephrine and tobacco, and he remained normotensive. His only residual deficit was minimal right arm weakness, which had been noted during his hospitalization.

This is the first report linking an inhaled over-the-counter sympathomimetic to ICH. While it is possible his excessive epinephrine use did not cause the thalamic hemorrhage, we were unable to identify risk factors such as chronic hypertension, illicit drug use, or a hemorrhagic disorder. He did smoke and take an occasional ibuprofen. Since cigarette use slightly increases the risk of ICH and ibuprofen can induce platelet dysfunction, it is possible these factors played a role in his stroke [2]. Perhaps the excessive use of inhaled epinephrine, combined with smoking and ibuprofen, led to the ICH. Certainly, the increased use of inhaled epinephrine appears temporally related to the stroke.

There are many case reports describing ICH after taking over-the-counter sympathomimetics, and sales of two of these drugs, phenylpropanolamine and ephedra, were halted in the US after

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more extensive studies associated these medications with ICH [3, 4]. Both are oral preparations, but intranasal sympathomimetics such as oxymetazoline and phenylephrine have also been linked to ICH [1]. Similar to intranasal delivery systems, inhaled medications can reach high levels in the blood. Inhaled epinephrine has been shown to increase plasma levels of epinephrine, and this is associated with elevations in heart rate and systolic blood pressure [5]. The proposed mechanisms by which over-the-counter sympathomimetics lead to ICH include surges in blood pressure, induction of vasculitis, and stimulation of cerebral vasospasm [1]. Since inhaled epinephrine has systemic sympathomimetic effects, it too could lead to ICH via one of these mechanisms.

Despite multiple reports associating over-the-counter sympathomimetics and stroke, controversy still exists as to whether these drugs increase the risk of ICH [6, 7]. A randomized controlled trial to fully explore this association is unlikely to occur because an extremely large study population would be needed to evaluate such a rare event. We feel the current evidence raises significant concern regarding the association between over-the-counter sympathomimetics and ICH. This potential public health problem warrants further investigation, and inhaled epinephrine should be included with other over-the-counter sympathomimetics when evaluating this issue in the future.

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PLACEBO-CONTROLLED EVAULATION OF THE SPEED OF ONSET OF EPINEPHRINE METERED-DOSE AEROSOL (PRIMATENE ® MIST) IN MILD TO MODERATE ASTHMATICS.

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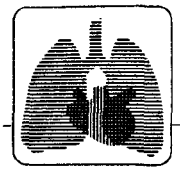
According to current recommendations for management of mild to moderate asthma, aerosolized adrenergic bronchodilators should be used primarily on an as-needed basis for relief of acute symptoms of asthma. Since speed of onset of bronchodilation is a desirable property of adrenergic agents used principally as rescue medication, we systematically measured the time of onset and time to peak action of Primatene® Mist (E), a commonly used over-the-counter metered-dose inhaler (MDI) that delivers 0.3 mg epinephrine bitartrate (0.16 mg epinephrine base) per inhalation, in comparison with an identical-appearing placebo (P) inhaler, in 24 subjects (age 37.4 ± 13.7 [SD] yrs) with mild to moderate asthma (screening FEV_1 64.5 ± 11.1% pred). A double-blind, random-order, two-period crossover design was used. Following screening evaluation documenting a ≥15% improvement in FEV_1 after 1 inhalation of E, subjects were studied on 4 separate days approximately 1 wk apart during which they underwent forced expiratory spirometry (days 1 & 3) or plethysmographic measurements of specific airway conductance (SG_{aw})(days 2 & 4) before and serially following 1-2 inhalations of either E or P administered in random order. Subjects withheld aerosolized bronchodilators for ≥ 8 hrs, oral β-agonists for ≥12 hrs and theophylline for 24-48 hrs prior to testing and demonstrated stability of baseline FEV_1 (≤10% variability) across test days. Following the first inhalation of the assigned drug, on days 1 & 3, spirometry was repeated at 15, 30 & 45 sec and at 1, 1.25, 1.5, 2, 3, 4, 5, 10, 15, 20 & 30 min, and on days 2 & 4, plethysmography was repeated at 15 & 45 sec and at 1.25, 1.65, 2.25, 3, 4, 5, 10, 15, 20 & 30 min. A second inhalation was administered 1 min after the first and just prior to the 1-min or 1.25-min test on spirometry & plethysmography days, respectively. **Results:** Clinically significant improvement in FEV_1 and SG_{aw} was defined as an increase of ≥ 15% and ≥ 50% above baseline, respectively. At 15 sec after 1 inhalation, 11/24 and 12/24 subjects receiving E and only 1/23 and 0/24 subjects receiving P exhibited significant improvement in FEV_1 and SG_{aw} respectively (differences between E and P, P<0.004: Gart test). Mean absolute (and percent) increases [± 1 SEM] in FEV_1 and SG_{aw} at 15 sec after 1 inhalation were 390±60 ml (16.8 ± 2.6%) and 0.04 ± 0.01 sec^{-1} cm H_2O^{-1} (49.3 ± 9.2%), respectively, after E, and (-120 ± 7 ml (-6.1 ± 2.9%) and –0.03 ± 0.01 sec^{-1} cm H_2O^{-1} (-26.0 ± 3.7%), respectively, after P (differences between E and P, P < 0.0001). Mean peak absolute (and percent) increases in FEV_1 and SG_{aw} were 800 ± 80 ml (34.5 ± 3.3%) and 0.12 sec^{-1} cm H_2O^{-1} (156 ± 18%), respectively, after E and 180 ± 60 ml (6.9±2.5%) and 0.02±0.01 sec^{-1} cm H_2O^{-1} (23.9±6.1%), respectively, after P (differences between drug days, P<0.0001). After E, the mean time to peak increase in FEV_1 and SG_{aw} was 7.5 ± 7.8 (SD) min and 9.3 ± 8.0 min, respectively. **Conclusion:** Compared to placebo, 1 inhalation of epinephrine MDI (Primatene ® Mist) produces clinically significant bronchodilation within 15 sec in subjects with mild to moderate asthma. With 2 inhalations administered 1 min apart, average time to peak bronchodilation is < 10 min.

Am Rev Respir Dis 1994; 149:A204



special report

Safety of Over-the-Counter Inhalers for Asthma*

Report of the Council on Scientific Affairs

Barry D. Dickinson, PhD; Roy D. Altman, MD; Scott D. Deitchman, MD, MPH; Hunter C. Champion, MD; for the Council on Scientific Affairs, American Medical Association†

The occasional use of over-the-counter (OTC) epinephrine inhalers appears to be safe and effective when used according to labeled instruction by individuals with mild, intermittent asthma. However, gross misuse of these products can cause severe adverse reactions, including death. Limited survey data suggest that approximately 20% of individuals using OTC epinephrine inhalers have mild-to-moderate persistent asthma. According to recent consensus guidelines, these individuals should be under a physician's care and receiving corticosteroid therapy. If these products continue to be marketed, labeling should be strengthened to better educate users about appropriate and inappropriate use of OTC epinephrine inhalers intended for patients with mild, intermittent asthma. ***(CHEST 2000; 118:522–526)***

Key words: administration; adrenergic β-agonists; asthma; drugs; epinephrine; inhalation; inhaler; nonprescription; over-the-counter; product labeling; safety

Abbreviations: AMA = American Medical Association; CFC = chlorofluorocarbon; FDA = US Food and Drug Administration; OTC = over-the-counter

While occasional use of over-the-counter (OTC) epinephrine inhalers appears to be safe and effective when used according to labeled instruction by individuals with mild, intermittent disease, gross misuse or abuse of these products can cause severe adverse reactions, including death. This report evaluates the available evidence on the safety (including product labeling) and efficacy of OTC epinephrine inhalant devices intended for the treatment of mild asthma.

*From the Council on Scientific Affairs, American Medical Association, Chicago, IL
Presented as Report 2 of the Council on Scientific Affairs at the 1999 Annual Meeting of the American Medical Association. The recommendations, as amended, were adopted as AMA policy, and the remainder of the report was filed
†A complete list of members and staff at the time of this report is located in the Appendix
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Materials and Methods

Published studies from the years 1966 to 1998 were identified through a MEDLINE search of English-language articles, using the key words *epinephrine, adrenergic beta agonists, asthma, administration, inhalation,* and *drugs, nonprescription* A total of 16 articles were retrieved. Further information was obtained from a search of the file, F-D-C Reports, in the Lexis-Nexis database using the key words *epinephrine, over-the-counter,* and *inhaler,* yielding 12 reports; and from the final monograph published by the US Food and Drug Administration (FDA) for OTC bronchodilator drug products

History and Status of OTC Epinephrine Inhalers

OTC epinephrine inhalers were first marketed in the United States in the 1960s In 1976, the FDA published an advance notice of proposed rule making to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, in conjunction with recommendations offered by the Advisory Review Panel responsible for evaluating data on the active ingredients in this drug class.

The tentative final monograph for OTC bronchodilator products was published in 1982,[1] in which the FDA concluded the following:

Epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic; since renamed racepinephrine hydrochloride)

medication has been reported to cause cardiomyopathy and catecholamine-induced sialadenosis [10,11] The latter is characterized by persistent symmetric enlargement of the parotid glands, with infrequent involvement of the submandibular salivary glands. A review of spontaneous adverse reaction reports from 1975 to 1997 found 286 reactions and 13 deaths associated with the use of an epinephrine inhaler. Three of the deaths were believed to be caused by a concomitant medical condition. In the 10 remaining reports, the relationship of epinephrine to the fatal outcome could not be established. Confounding factors were substance abuse, product misuse, and nonrespiratory system-related conditions. The manufacturer estimated that > 115 million Primatene Mist inhalers had been sold in the time frame covered by this review (Barbara Wolf, RPh; personal communication; February 2, 1999). Two deaths associated with abuse of epinephrine inhalers (brand not specified) appeared in poison control data reported from 1994 to 1998.[12,13]

Associations between the use of inhaled β-agonists and asthma morbidity and mortality have been reported, especially in the 1960s following the introduction of isoprenaline forte, and in New Zealand in 1976 following the introduction of fenoterol.[14,15] These agents were supplied in what are now recognized as high-dose formulations and, like epinephrine, they activate β_1 as well as β_2 receptors To our knowledge, no other β-agonists have been implicated in asthma mortality epidemics. However, increasing asthma mortality over the last 2 decades has led some to suggest that the regular use of inhaled β-agonists (as a class effect) may be a contributory factor, by increasing asthma severity in some patients. This concept remains unproven, but controversial [16–20] In any event, it is not likely to apply to OTC epinephrine inhalers because of their weak potency

Of greater concern is the possibility that patients with mild-to-moderate persistent asthma may rely on OTC bronchodilators and avoid seeking medical care, which may ultimately lead to disease progression and increased morbidity Many deaths from asthma are believed to be caused by inadequate or delayed treatment, and therefore are potentially preventable.[21] In countries where a more potent inhaled β-agonist (salbutamol) is available OTC, purchase is associated with lower rates of physician consultation, undertreatment of asthma, and less use of prescription asthma medications, especially inhaled corticosteroids [22–24]

Whether nonprescription availability of OTC epinephrine inhalers in the United States causes patients with mild-to-moderate persistent asthma to self-medicate and delay seeking needed medical care is unknown Delaying physician consultation would have more to do with the patient's behavior than with the safety and efficacy of OTC inhalers Some survey data on the use of epinephrine inhalers are available In a survey involving > 300,000 households commissioned by Whitehall-Robins Healthcare to determine demographic patterns and use profiles of Primatene Mist,[25,26] 37% of patients with asthma reported using prescription and nonprescription products at different times About two thirds of this subgroup used the OTC product because their prescription had run out, and one third because a prescription was unavailable. For other demographic features, see Table 2.

Such surveys are subject to recall bias and, while providing useful population data, do not allow the type of statistical power and detail that would be available by conducting a study of consumers at the time they purchase epinephrine inhalers. Nevertheless, these results suggest that the majority of individuals who report using Primatene Mist represent a population (with mild asthma) and use the drug in accordance with labeled directions; however, approximately 20% also fulfill at least one criterion for asthma severity indicating the presence of mild-to-moderate persistent disease that warrants close physician oversight and treatment with inhaled corticosteroids (nocturnal symptoms ≥ 1 week, requirements for urgent care).[27,28]

This interpretation is in agreement with the findings of a smaller analytic study that assessed demographic and clinical covariates of self-treatment with OTC asthma medications [29] This study recruited participants who exclusively used OTC asthma medications (n = 15), used both prescription and nonprescription asthma medications (n = 13), or used prescription drugs exclusively (n = 22) Except for one subject, all participants who reported using OTC asthma medications were using epinephrine inhalers Most OTC users were of male gender. Pulmonary function and self-assessed disease severity were similar among groups. However, OTC users' self-assessment of their disease severity was not correlated with the extent to which epinephrine inhalation reversed airflow obstruction Thus, in this study, OTC bronchodilator users perceived less disability from asthma, but did not differ from prescription users in objective measures of disease severity. Other measures (history of hospitalization, corticosteroid use) indicated that OTC use of epinephrine inhalers was not restricted to persons with only mild, intermittent asthma A later follow-up study by the same investigators confirmed the relationship between male gender and purchase of OTC epinephrine (or ephedrine) products, but found no association between use of such products and risk of hospitalization due to asthma.[30]

Concerns About the Availability of OTC Epinephrine Inhalers

Because of recent trends toward increased asthma morbidity and mortality, a critical reexamination of current treatment

Table 2—*Demographic Features of Patients Using Primatene Mist

Parameters	Nationwide Household Survey
No of users (n = 363)	1 8% of individuals with asthma used an OTC asthma medication; 1 3% of these were PM
Frequency of use	36% < 1/mo; 35% 1 to 4 times/mo; 29% > 4 times/mo
Frequency of asthma attacks	36% < 1/mo; 41% 1 to 4/mo; 23% > 4 time/mo
Lost work or school days due to asthma	86% none; 12% 1 to 5 d; 2% > 5 d
Sleep disturbance	57% < 1/mo; 22% < 3/mo; 21% ≥ 1/wk
Requirements for urgent care in previous 12 mo	78% none; 15% 1 to 3 times; 7% > 4 times
Physician diagnosis of asthma	86%
Had discussed use of PM with physician	52%; 13% reported doctor had recommended PM use
Percent of PM users also using prescription asthma drugs	37%, but at different times

*Adapted with permission from Comino et al[24] and Redman and Druce [25] PM = Primatene Mist.

practices and their possible role in adverse short-term and long-term patient outcomes has occurred. This has logically been extended to the OTC arena

Those who oppose the OTC availability of epinephrine inhalers (or any other asthma medication) believe that the availability of asthma medications discourages the implementation of patient education programs, and the use of objective monitoring by limiting contact between patients and qualified medical personnel The National Heart, Lung, and Blood Institute Asthma Treatment Guidelines stress the need for physician monitoring of asthma patients, the importance of patient education on the use of metered-dose inhalers and peak flow monitors, and the use of the stepped-care approach, which favors earlier use of prescription anti-inflammatory medications.[28] According to this viewpoint, the continuing availability of OTC drugs is a step in the wrong direction, sending the wrong message that asthma is not a serious disease that needs close attention.

Compared with prescription β-agonist bronchodilators, epinephrine inhalers are less potent and shorter acting Conceivably, this should limit the use of the drug by patients with more serious asthma, and also the potential for serious systemic effects, as long as the drug is used according to directions contained in the product labeling. Furthermore, little evidence has been formally presented to indicate that OTC epinephrine metered-dose inhalers are causing any harm to the targeted patient group (*ie*, those with mild, intermittent disease) Additionally, the availability of at least one OTC asthma quick relief medication allows individuals with mild asthma and those who do not have access to the health-care delivery system to self-medicate

Conclusion

The occasional use of OTC epinephrine inhalers appears to be safe and effective when used according to labeled instruction by individuals with only mild, intermittent disease. Individuals who grossly misuse or abuse these products are subject to severe adverse reactions, including death. However, limited survey data suggest that approximately 20% of individuals using OTC epinephrine inhalers have mild-to-moderate persistent asthma. According to recent consensus guidelines, these individuals should be under a physician's care and receiving corticosteroid therapy.

Recommendations

The following statements, recommended by the Council on Scientific Affairs, were adopted as American Medical Association (AMA) policy in June 1999.

1. The AMA supports strengthening the product labeling for OTC epinephrine inhalers to better educate users about patterns of inappropriate use; to include clear statements that the use of OTC inhalers can be dangerous; to urge users to seek medical care if symptoms do not improve, or if they meet criteria for the presence of persistent disease; and to encourage explicit discussions with physicians about dosage when these products are used

2. The AMA encourages the FDA to reexamine whether OTC epinephrine inhalers should be removed from the market.

3. In the event that these products continue to be marketed OTC, further information should be obtained to determine whether OTC availability is a risk factor for asthma morbidity and mortality

Appendix

Members and staff at the time of this report include the following: Joseph A. Riggs, MD, Haddon Field, NJ (Chair); Myron Genel, MD, New Haven, CT (Chair-Elect); Roy D Altman, MD, Miami, FL; Hunter C. Champion, MD, New Orleans, LA; Ronald M. Davis, MD, Detroit, MI; Scott D Deitchman, MD, MPH, Duluth, GA; J Chris Hawk III, MD, Charleston, SC; John P Howe III, MD, San Antonio, TX; Mohamed Khaleem Khan, MD, PhD, Boston, MA; Nancy H Nielsen, MD, PhD, Buffalo, NY; Michael A Williams, MD, Baltimore, MD; Donald C. Young, MD, Iowa City, IA Staff: Barry D Dickinson, PhD (Secretary); James M. Lyznicki, MS, MPH (Assistant Secretary); Marsha Meyer (Editor), Chicago, IL

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Comparison of subcutaneous injection and high-dose inhalation of epinephrine—Implications for self-treatment to prevent anaphylaxis

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The plasma concentrations of epinephrine were determined in healthy subjects administered epinephrine by subcutaneous injection of 0.5 mg or inhalation of 1.5 to 4.5 mg (10 to 30 inhalations from a metered-dose aerosol). The absorption of injected epinephrine was variable and in several cases very slow. The individual maximum values for epinephrine in plasma were 4.65 ± 1.09 (range 0.74 to 8.31) nmol/L, and these maxima were attained 5 to 120 minutes after injection. Inhaled epinephrine was rapidly and dose dependently absorbed. Ten inhalations resulted in 2.72 ± 0.84 (0.75 to 5.67) nmol/L within 5 minutes and 20 inhalations resulted in 7.19 ± 1.78 (2.10 to 13.83) nmol/L with rapid increases and maxima within 20 minutes in seven of eight subjects. Gastrointestinal side effects were dose limiting when epinephrine was administered by inhalation. Our results indicate that inhalation of 2 to 3 mg of epinephrine produces rapid increases of epinephrine concentrations in plasma to levels that have previously been demonstrated to counteract bronchoconstriction induced by inhaled allergen in subjects with asthma. Inhalation has several advantages over injection for self-administration of epinephrine, e.g., in patients who are allergic to insect (Hymenoptera) stings. Apart from the absorption being more rapid, the locally high concentrations of epinephrine in the airways should be advantageous, since bronchoconstriction is one of the life-threatening phenomena of the anaphylactic reaction. This route of administration is also simple for the patient. (J ALLERGY CLIN IMMUNOL 78:1174-9, 1986.)

Individuals who have once suffered an anaphylactic shock or a severe anaphylactoid reaction after a sting from an insect of the Hymenoptera family (honey bees and wasps) are usually prescribed drugs for self-administration in case of a new sting from the same type of insect.[1-3] The patients are instructed to use these first aid measures immediately after a sting to prevent the development of a generalized anaphylactic reaction. Perhaps the most important of the prescribed drugs is epinephrine, which traditionally has been used in the treatment of already established allergic or anaphylactic reactions.[4] Potentially beneficial effects of epinephrine include an antiallergic action, bronchodilatation, reduction of mucosal swelling,[5] and, perhaps, cardiovascular actions. An important question concerns how patients should self-administer epinephrine in the face of a threatening reaction to the insect sting. To be able to prevent or ameliorate the expected anaphylactic reaction, it appears imperative that the absorption of epinephrine is rapid and efficient.

Two "schools" exist with regard to self-administration of epinephrine. One school advocates administration of epinephrine by injection[1, 2] and the other, administration by inhalation from a metered-dose inhaler.[3, 6] Important arguments favoring the latter route of administration are that locally high concentrations of epinephrine are achieved in the airways and that the aerosol device is easy for the patient to handle. There is, however, no satisfactory documentation concerning the plasma concentrations of epinephrine attained after administration either by subcutaneous injection or by the metered-dose aerosol inhalation method. Furthermore, suitable doses for inhalation of epinephrine have not been established. The aims of this study were, therefore, first, to compare the time courses for absorption of epinephrine from a subcutaneous depot and after inhalation and, second, to determine the levels of epinephrine reached in

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plasma after administration by these two routes in doses which may be appropriate for use in ordinary clinical practice.

MATERIAL AND METHODS

Subjects

Twelve healthy subjects (nine women and three men), aged 25 to 54 years (mean 38 years), participated after informed consent. Four of the subjects received epinephrine in all three dosage regimens of the main study. Two subjects received two dosages of epinephrine, and six subjects took part in trials with one dosage only. The study protocol was approved by the local Ethics Committee.

Procedure and methods

All experiments commenced at 8 A.M. with the subjects fasting since the night before. When two or more trials were performed in the same subject, an interval of at least 1 week was obligatory between trials.

After application of an indwelling antecubital venous catheter, ECG electrodes, and a blood pressure cuff, the subject rested for 30 minutes in the recumbent position. Epinephrine was then administered either by subcutaneous injection of 0.5 mg (Adrenalin, ACO, Solna, Sweden, 1 mg/ml) or as 10 or 20 inhalations, respectively, from a metered-dose aerosol. For these inhalations, metered-dose aerosols (epinephrine Medihaler, 3M Riker, Loughborough, Great Britain) delivering 0.15 mg of epinephrine per inhalation were used. Consequently, 10 inhalations corresponded to 1.5 mg, and 20 inhalations corresponded to 3.0 mg epinephrine.

Before the study proper, some pilot experiments were performed to establish suitable inhalation doses for the main study. The doses used in the pilot study varied from three inhalations (a dose often used in the therapy of subjects with asthma) to 30 inhalations of epinephrine. Some of these results will also be reported.

All subcutaneous injections of epinephrine were administered by the same investigator and in the same area on the upper lateral part of the thigh, to minimize variability. Before the trials all subjects were carefully instructed with regard to inhalation technique, which was practiced with a placebo device. Aerosols were inhaled as follows: Each aerosol puff was triggered at the beginning of a slow inhalation after a maximal exhalation. The subject held his/her breath at maximal inspiration until 10 seconds had elapsed from the start of the inhalation. Between inhalations the subjects were instructed to breathe normally for 10 seconds. Thus, the total time required for each puff was 20 seconds. Consequently, 10 puffs required 3 minutes, and 20 puffs required 6 minutes.

The following variables were recorded: heart rate, blood pressure, blood glucose, and plasma epinephrine. These variables were all measured immediately before and every 5 minutes during the first 20 minutes, then every 20 minutes to 120 minutes, and, finally, 150 minutes after the dose was administered.

Heart rate was determined by brachial pulse counting. In addition, a tape-recorded continuous ECG was used to detect possible arhythmias. Blood pressure was measured by means of an aneroid manometer with a conventional brachial cuff. Blood glucose was determined by means of a commercially available glucose oxidase technique (Reflomat, Boehringer-Mannheim AG). Venous blood samples for analysis of plasma epinephrine were taken through an indwelling plastic catheter in an antecubital vein. The samples were collected on ice in plastic tubes containing ethylenediaminetetraacetic acid (10 mmol/L final concentration). After centrifugation at 4° C, the plasma was removed and stored at −70° C until it was analyzed. Plasma epinephrine was determined by high-performance cation exchange liquid chromatography with electrochemical detection, as described and validated previously.[7,8]

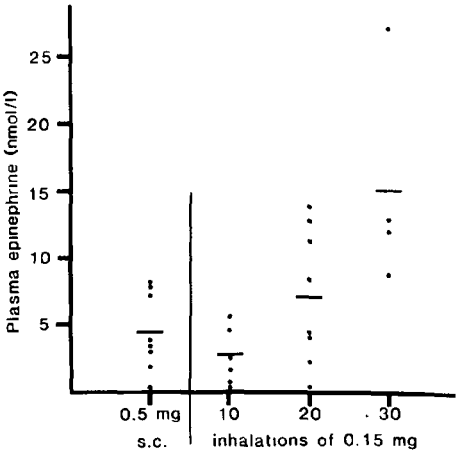

FIG. 1. Individual maximum values for venous plasma epinephrine concentrations after subcutaneous injection or inhalation, irrespective of the time at which these maxima were reached. There was a linear relationship between dose of inhaled epinephrine and the peak concentration in plasma ($r = 0.69$; $p < 0.01$). Twenty and 30 inhalations resulted in significantly higher peak concentrations than 10 inhalations ($p < 0.05$ for both).

Statistical analyses

Results are presented as mean values ± SEM in the text and illustrations. Significance levels for changes from baseline (i.e., time 0) were assessed by Student's t test for paired variates. Differences in peak concentrations achieved at the different dose levels were assessed by Student's t test for unpaired observations. In addition, the relationship between dose and plasma level was evaluated by linear regression analysis.

RESULTS

Plasma epinephrine concentrations

After *subcutaneous injection* of 0.5 mg of epinephrine, the plasma concentrations of epinephrine increased from basal values of 0.35 ± 0.05 nmol/L to a maximum of 4.65 ± 1.09 (range 0.74 to 8.31)

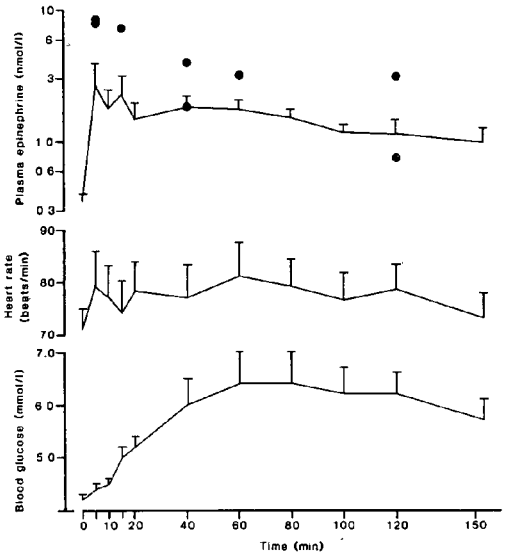

FIG. 2. Venous plasma epinephrine concentrations (on a logarithmic scale), heart rate, and blood glucose concentrations basally (time 0) and after subcutaneous injection of 0.5 mg of epinephrine. Mean values ± SEM are for eight subjects. The individual maxima with regard to epinephrine concentrations have been marked with *dots*.

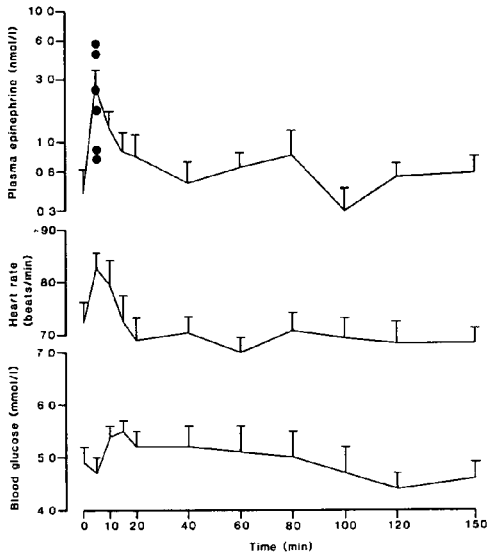

FIG. 3. Responses to 10 inhalations of epinephrine (i.e., 1.5 mg delivered during 3 minutes) from a metered-dose aerosol. Mean values ± SEM are for six subjects. Symbols same as in Fig. 2.

nmol/L (Fig. 1). These values refer to each individual's maximum plasma epinephrine level, irrespective of the time at which the maximum was reached. Three subjects reached their maximum levels within 15 minutes, but five of eight subjects did not achieve their maxima until 40 to 120 minutes after the injection (Fig. 2). In the group as a whole, the plasma epinephrine concentrations were significantly increased during the interval 40 to 150 minutes after injection.

When epinephrine was administered as *10 inhalations* (i.e., 1.5 mg, administered during 3 minutes), maximum plasma concentrations of 2.72 ± 0.84 (range 0.75 to 5.67) nmol/L were attained (Fig. 1). All six tested subjects reached their maximum values within 5 minutes, and significant increases in plasma epinephrine concentrations were found during the interval 5 to 10 minutes after commencing inhalations (Fig. 3).

After *20 inhalations* of epinephrine (i.e., 3.0 mg, administered during 6 minutes), maximum plasma epinephrine concentrations of 7.19 ± 1.78 (range 2.10 to 13.83) nmol/L were attained (Fig. 1). The increases were rapid, and seven of eight subjects reached their maxima within 20 minutes after commencing inhalation (Fig. 4). Significant elevations of epinephrine in plasma were found during the period 5 to 40 minutes after commencing inhalations.

In addition, results from the pilot studies in which the dose of *30 inhalations* (4.5 mg) was tested are illustrated in Figs. 1 and 5. This dose was rejected because of side effects (see below). The dose of three inhalations failed to elevate plasma epinephrine concentrations, as they remained below 0.2 nmol/L (not presented).

Heart rate

Subcutaneous injection of epinephrine caused a slight elevation of heart rate (<10 bpm on the average) immediately after injection, and a second, very sluggish peak, at about 60 minutes (Fig. 2). All three doses of inhaled epinephrine caused short-lasting (5 to 20 minutes) elevations of heart rate that tended to be dose dependent (Figs. 3 to 5).

Blood pressures

All modes of epinephrine administration resulted in rapid (maximum values at 5 to 10 minutes) and short-lasting increases of systolic blood pressure (not presented). The most pronounced effect was noticed after 30 inhalations of epinephrine, which resulted in an increase of 25 ± 3 mm Hg.

Diastolic blood pressures did not change significantly with either of the dosage regimens. The mean changes were −6 mm Hg 40 minutes after 0.5 mg was administered subcutaneously, −5 mm Hg 120 minutes after 10 inhalations, −4 mm Hg 15 minutes

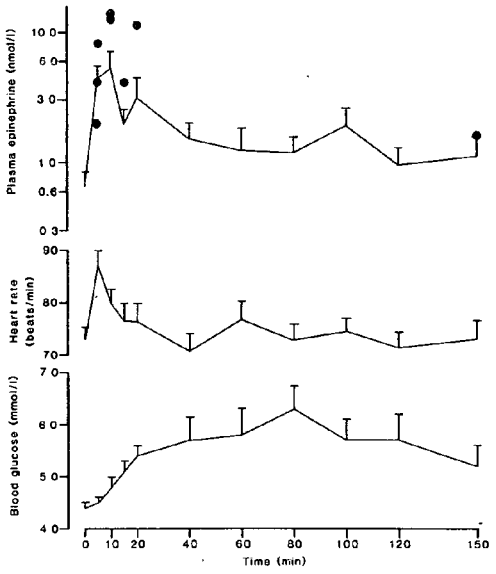

FIG. 4. Responses to 20 inhalations of epinephrine (i.e., 3.0 mg delivered during 6 minutes) in eight subjects. Symbols same as in Fig. 2.

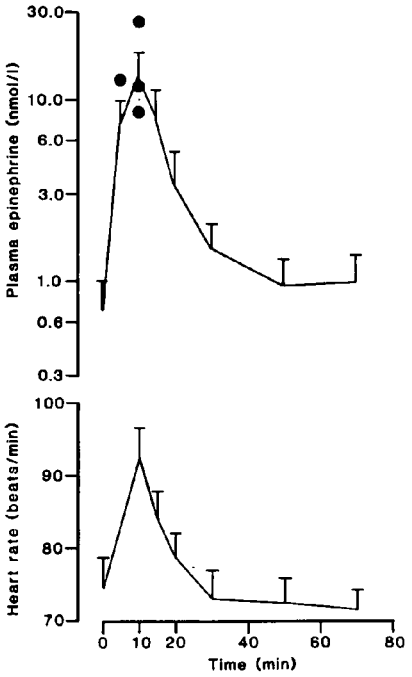

FIG. 5. Venous plasma epinephrine concentrations and heart rates in four subjects who received 30 inhalations of epinephrine (i.e., 4.5 mg delivered during 10 minutes) in the pilot experiments. This dose level was not studied further because of gastrointestinal side effects. Symbols same as in Fig. 2.

after 20 inhalations, and +10 mm Hg 10 minutes after 30 inhalations of epinephrine.

Blood glucose

After subcutaneous injection of epinephrine, there was a gradual increase of blood glucose levels from 4.2 ± 0.3 to 6.4 ± 1.6 mmol/L at 60 minutes (Fig. 2). This elevation of blood glucose levels then persisted throughout the experiment. Inhalation of the low dose (10 inhalations) of epinephrine resulted in a more rapid, but considerably less pronounced, increase in blood glucose concentrations (Fig. 3). Twenty inhalations of epinephrine resulted in a blood glucose response that was very similar to the one observed after subcutaneous injection of epinephrine, with respect to both the time course and magnitude (Fig. 4). Thus, the maximum level (6.3 ± 1.0 mmol/L) was reached 80 minutes after these inhalations.

Side effects

After *subcutaneous injection* of 0.5 mg of epinephrine, three of eight subjects reported tremor, and two subjects reported palpitations. Both symptoms persisted approximately 2 hours.

After *inhalation* of epinephrine, 9/14 subjects experienced tremor, which was rapid in onset and subsided after 5 to 20 minutes. After large doses of inhaled epinephrine, gastrointestinal symptoms were experienced. Twenty inhalations caused general gastrointestinal symptoms with slight nausea in two of eight subjects and strong nausea in two individuals, one of whom also vomited. In three of these subjects, the reactions subsided within approximately 80 minutes after administration. One subject with strong nausea, however, had moderate persisting symptoms for several hours. The largest dose tested (30 inhalations) caused even more marked gastrointestinal symptoms of the same character.

No cardiac arrhythmias were observed on the tape-recorded ECGs after either of the routes or dosages of epinephrine.

DISCUSSION

Intravenous injections of antigen to sensitized animals evoke rapidly occurring anaphylactic reactions that trigger rapid and marked elevations of plasma epinephrine concentrations.[9, 10] Similarly, case reports have demonstrated that the cardiovascular responses to anaphylaxis induced by intravenous injections of histamine-releasing drugs in man are extremely rapid and that these reactions trigger the release of endog-

enous epinephrine, resulting in epinephrine levels of 5 to 10 nmol/L in plasma within 1 to 2 minutes after administration of the drug.[11, 12] Since the anaphylactic reaction to an insect sting may develop rapidly, it appears important to choose a dose and a route of administration that results in sufficiently high plasma concentrations of epinephrine within minutes after self-administration if a preventive or ameliorating effect is to be obtained.

The present study demonstrates that the absorption of epinephrine from subcutaneous tissue on the thigh is extremely variable and may be very slow in some individuals. Thus, the maximal epinephrine levels achieved varied between 0.7 and 8 nmol/L, and these maxima were attained at time points from 5 to 120 minutes after injection. Our findings of poor and variable absorption of subcutaneously administered epinephrine are in agreement with previous findings in the rat.[9] It is not surprising that the absorption of epinephrine from a subcutaneous depot is low and variable in view of the well-established use of epinephrine as a local vasoconstrictor that delays the absorption of local anesthetics from tissue depots for example.

In the treatment of asthma, 0.5 to 1 mg of epinephrine, subcutaneously, has been advocated as the optimal dose.[13, 14] However, our results demonstrate relatively low plasma epinephrine levels (about 1.5 to 2 nmol/L on the average) after the injection of 0.5 mg. It therefore appears reasonable to advocate larger doses and/or the intramuscular or intravenous route when anaphylactic reactions are treated[4, 13] and perhaps also when asthma is treated. The intramuscular route does not appear to have been advocated for self-treatment and may be less safe than the subcutaneous route in inexperienced hands. The present results, however, cast considerable doubt on the use of the subcutaneous route of administration for self-treatment with epinephrine to prevent anaphylactic reactions.

Inhaled epinephrine, by contrast, was rapidly and dose dependently absorbed. It is noteworthy that considerably larger doses than those recommended in the treatment of asthma were required to elevate plasma epinephrine concentrations to levels that might have a protective effect in connection with exposure to an allergen. Thus, approximately 20 inhalations (3 mg) of epinephrine were required to achieve plasma concentrations on the order of 6 nmol/L, which is a level previously demonstrated to counteract allergen-induced bronchoconstriction.[5] There was considerable interindividual variation with regard to the epinephrine concentrations achieved in plasma after inhalation. However, the rate of absorption was more rapid and considerably less variable than after subcutaneous injections, as the peak concentrations of epinephrine were achieved within 5 to 10 minutes in practically every experiment.

Our findings are in agreement with results from experiments with dogs demonstrating a rapid and efficient absorption of epinephrine after endotracheal instillation.[15, 16] Endotracheal administration of epinephrine has also been used successfully in a couple of cases of human anaphylaxis.[17]

Hoehne et al.[18] determined the urinary excretion of epinephrine after subcutaneous injection (0.5 mg) and inhalation (2.4 mg) of epinephrine. They found a clearly enhanced epinephrine excretion after injection but not after inhalation and, therefore, advocated the use of inhaled epinephrine only when upper airway obstruction was being treated.[18] Differences between their study and the present study may, in part, be due to differences in inhalation technique, since Hoehne et al.[18] administered their 15 inhalations more rapidly. It is known that <10% of an inhaled dose reaches the deeper respiratory tract even with a good inhalation technique.[19] Our results support the use of inhaled epinephrine for self-administration, provided that a good inhalation technique is used, since, presumably, efficient plasma levels of epinephrine appear to be attained more rapidly with this technique than with subcutaneous injection.

Apart from the greater rapidity with which the epinephrine is absorbed from the airways, it is more convenient for the patient to handle a metered-dose aerosol than equipment for injections. Furthermore, it may be a considerable advantage to obtain high concentrations of epinephrine in the airways, since Barnard[1] found that most deaths (69 of 100 investigated cases) after insect stings appeared to be related to respiratory obstruction. Thus, local antiallergic, bronchodilating, and mucosal-decongesting effects of epinephrine in the airways should be beneficial. It would, however, be advantageous to use an aerosol delivering a larger amount of epinephrine per dose, since the time required to administer 1.5 to 3 mg with the currently available metered aerosol is rather long, if a good inhalation technique is to be ensured.

The cardiovascular responses noted in the present study were rather small and consisted of an initial short-lasting tachycardia after 10 to 20 inhalations of epinephrine. After subcutaneous injection, there was a biphasic heart rate response. The initial increases in heart rate may, in part, have been evoked by stress, anticipation, or pain in connection with the injection. The small heart rate responses are in accordance with our previous experience using intravenous infusions of epinephrine.[20] The more protracted increases in

blood glucose found after subcutaneous injection or 20 inhalations of epinephrine demonstrate that the effect of epinephrine is long lasting after these procedures.

The most important side effect observed in the present study was gastrointestinal discomfort with nausea and occasional vomiting after large doses (3 to 4.5 mg) of inhaled epinephrine. This may be related to local effects of epinephrine on the gastrointestinal tract because the symptoms appeared rather late, and it may be presumed that >90% of the dose was swallowed.[19] Furthermore, this type of side effect was not noted after subcutaneous injection. Well-known side effects observed after both routes of administration were mild tremor and palpitations in some individuals. This did not cause much discomfort to the subjects. Thus, the gastrointestinal side effects are dose limiting when epinephrine is inhaled.

Even though epinephrine is considered to be the drug of choice for use in connection with anaphylactic or threatening anaphylactic reactions, very little is known about what doses or plasma concentrations are required in this context. In subjects with asthma, infusion of epinephrine to the plasma concentrations observed after 20 inhalations of epinephrine in the present study has been demonstrated to counteract bronchoconstriction induced by inhaled allergen.[5] The efficacy of circulating epinephrine with regard to the other manifestations of anaphylaxis is not known. Evaluation of the clinical effectiveness of epinephrine would require a comparison of the effects of epinephrine and placebo in allergen-provoked anaphylaxis. Such a study would entail considerable risks and would most likely be considered unethical. Thus, even if we have demonstrated a rapid absorption of epinephrine after inhalation, our results cannot yet be used as therapeutic guidelines without clinical documentation of possible protective effects in patients known to suffer reactions, e.g., after insect stings.

In summary, our study demonstrates that inhaled epinephrine is rapidly absorbed and may be suitable for self-administration to prevent anaphylactic reactions after insect stings. This method is easy for the patient to handle and has the advantage of providing high concentrations of epinephrine in the airways. The absorption of subcutaneously administered epinephrine was found to be too variable and slow to be advocated for this purpose. When epinephrine is inhaled, large doses (2 to 3 mg) and a good inhalation technique are, however, required to achieve rapid increases of plasma epinephrine to levels previously demonstrated to counteract allergen-induced bronchoconstriction. With inhaled epinephrine, late-occurring gastrointestinal side effects were dose limiting.

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Nonprescription Bronchodilator Medication Use in Asthma*

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Study objective: **Many persons with asthma self-medicate with widely available and potentially hazardous nonprescription medicines. This study assessed the demographic and clinical covariates of self-treatment with over-the-counter asthma medications (OTCs).**
Design and setting: **We conducted an analytical investigation using questionnaires and measures of lung function, comparing OTC and prescription medication users. We recruited adults with asthma by public advertisement.**
Subjects: **We studied 22 exclusive prescription asthma medication users, 15 exclusive OTC users, and 13 other subjects who combined prescription medication use with self-treatment with asthma OTCs. All but one OTC user self-medicated with a nonselective, sympathomimetic metered-dose inhaler.**
Results: **Taking income, access to care, and self-assessed disease severity into account, male gender was strongly associated with exclusive OTC use alone (odds ratio [OR]=8.9, 95% confidence interval [CI]=1.3 to 61) and mixed OTC-prescription medication use (OR=9.7, 95% CI=1.1 to 83). The covariates of income, access to care, and self-assessed disease severity provided significant additional explanatory power to the model of exclusive OTC use (model χ^2 difference 11.3, 5 *df*, $p<0.05$). Pulmonary function was similar among OTC and prescription medication users. However, prescription medication users' self-assessed asthma severity (mild compared to more severe) was associated with postbronchodilator reversibility of FEV_1 obstruction (6% vs 18% reversibility, $p<0.05$) while exclusive OTC users' self-assessed severity showed the reverse pattern (19% vs 8%, $p=0.2$).**
Conclusion: **Asthma education programs attempting to discourage unregulated bronchodilator use should give consideration to this profile of the "asthmatic-at-risk."**
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Key words: asthma; bronchodilator; nonprescription; OTC, PFT

Abbreviations: CI=confidence interval; MDI=metered-dose inhaler; OR=odds ratio, OTC=over-the-counter; PEFR=peak expiratory flow rate; PRE=prescription medication exclusively; PRE/OTC=both prescription and over-the-counter medications

Many persons with asthma self-medicate with widely available nonprescription drugs, especially over-the-counter (OTC) inhaled and orally administered bronchodilators. Although bronchodilators have an undisputed role in the short-term management of asthma, their unsupervised use presents potential risks. Use of sympathomimetics, and in particular nonspecific β-adrenergic receptor agonists, may result in adverse cardiovascular and CNS effects. Serious toxic reactions from nonprescription medications containing theophylline and ephedrine and from nonprescription inhaled epinephrine, although infrequent, does occur.[1-6] Poison control data, combining intentional overdose and misadventure, report more than 3,000 nontheophylline β_2-agonist cases annually and do include one recent inhaled epinephrine death.[7,8]

In contrast with sympathomimetic bronchodilators, anti-inflammatory medications such as corticosteroids are typically available only by prescription. Because inhaled corticosteroids are highly efficacious and have a very favorable side-effect profile,

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they are now a cornerstone of recommended treatment for adult asthma.[9,10] Indeed, the underutilization of anti-inflammatory therapy has been postulated as a possible remediable factor associated with recent increases in asthma mortality and morbidity.[11-16]

Reports from Australia have linked the use of nonprescription bronchodilators in adults with both the underutilization of inhaled corticosteroids and with infrequent physician consultation.[17-19] To our knowledge, however, there are no other published reports studying nonprescription medication use among persons with asthma and its impact on asthma management strategies. To address this knowledge gap, we carried out a descriptive analytic study seeking to characterize adults with asthma who self-treat their condition with nonprescription asthma medications. We wished to identify illness and demographic characteristics associated with nonprescription bronchodilator use, in particular socioeconomic variables that might impact access to care and psychosocial variables that might influence perceived need for care.

Materials and Methods

General Study Design

This was a descriptive and analytical study comparing clinical and demographic characteristics among persons who, over the 12 months prior to study, had used prescription asthma medications exclusively, nonprescription asthma medications exclusively, or who had used both prescription and nonprescription asthma medications. Demographic and clinical data were obtained through an interviewer administered, structured questionnaire. Pulmonary function was assessed by spirometry performed before and after administration of a bronchodilator. Ambulatory peak expiratory flow rates (PEFRs) were self-assessed over a 6-day period. The study was approved by the University of California San Francisco Committee on Human Research. The questionnaire and spirometry were performed in the Asthma Clinical Research Laboratory of the University of California San Francisco Medical Center.

Subject Recruitment

Using paid commercial newspaper advertisements, we recruited individuals who had used medication for the management of their asthma within the previous 12 months. Advertisements were placed in the *Bay Guardian*, a free weekly newspaper widely distributed throughout San Francisco, and in the *Chronicle*, the major morning daily newspaper in San Francisco. We intentionally employed advertisements worded such that asthmatics were recruited without regard to medication type or prescription status. We also ran supplemental advertisements in the same newspapers that specifically solicited persons who had used nonprescription asthma medications, either exclusively or in combination with prescription asthma medications, over the previous 12 months. We recruited sequentially until 50 participants, aged 18 to 50 years, were enrolled, including at least 25 who reported any use of nonprescription asthma medications. We did not retain data on potential participants who responded to our advertisement but did not use either prescription or nonprescription medication for asthma or who otherwise did not meet study criteria

Questionnaire

Subjects were administered a 15-min structured questionnaire by a single interviewer. The questionnaire was adapted from a more extensive, previously validated instrument.[20] Demographic information was ascertained, as well as employment and health insurance status, smoking history, and annual household income. A positive smoking history ("ever smokers") was defined as having smoked at least 100 lifetime cigarettes. Annual household income was assessed by ranges. Responses were analyzed as the middle value of the reported range, except for the range ≥$75,000 where the lower range value was used. Two subjects, exclusive OTC users, with missing data for income were each assigned an income value equal to the median value for the entire study group. Predictive models including income were run with and without these two subjects included.

Asthma symptoms and clinical parameters, subjects' perception of illness severity, and health services utilization were also assessed by questionnaire. Data solicited included age of onset of asthma symptoms, frequency of symptoms, age of physician diagnosis (if ever), subject-perceived asthma severity, access to a health-care provider for asthma management, and hospitalizations and emergency department visits for asthma exacerbations.

Information on subjects' use of asthma medications was solicited, including prescription and nonprescription oral and metered dose inhaler (MDI) bronchodilators, oral and MDI corticosteroids, and other asthma therapies. Subjects were specifically asked about use of 1) proprietary epinephrine (Primatene Mist or Bronkaid Mist), or generic MDI epinephrine; 2) proprietary albuterol (Proventil or Ventolin), or generic albuterol; 3) proprietary metaproterenol (Alupent or Metaprel), or generic MDI metaproterenol; and 4) Primatene or Bronkaid tablets or nonprescription and prescription theophylline and/or ephedrine-containing oral preparations. Nontraditional asthma therapies were defined as coffee, black tea, other caffeine-containing products, and herbal tea or tablets consumed with the specific intent to treat asthma.

Spirometry and PEFR Measurements

Subjects were asked to refrain from using a bronchodilator or from consuming any caffeine-containing beverage or food for at least 8 h prior to performing spirometry. Spirometry was performed on all subjects both before and after directly observed administration of albuterol by MDI. A total of 180 μg of albuterol was administered in two actuations of an MDI with a 1-min interval between actuations. Postbronchodilator spirometry was performed 15 min after the second actuation.

Spirometry was tested with the subject in the sitting position. We measured FEV_1 using a rolling seal spirometer according to American Thoracic Society standards.[21] Maximal flow-volume curves, using the rolling seal spirometer, were measured by analyzing flow and volume signals. Spirometry was performed either in the morning or afternoon, between 8 AM and 6 PM. We did not attempt to control for diurnal variation in lung function.

Subjects were instructed in the use of a standard-range peak flowmeter (MiniWright; Clement Clarke Inc; Columbus, Ohio) per published guidelines.[22] Subjects were asked to measure their PEFR twice daily for 6 consecutive days. They were instructed to make three consecutive peak flow measurements between 7 AM

and 9 AM and again between 7 PM and 9 PM and to record the PEFR values in a diary provided to them.

Classification of Subjects by Medication Use

Fifty subjects were divided into three groups based on their responses to questions on asthma medication use. Those subjects who had used prescription asthma medications *exclusively* over the preceding 12 months were classified as prescription medication (PRE) subjects (n=22). Those subjects who reported use of nonprescription epinephrine by MDI or use of nonprescription oral medications containing theophylline and/or ephedrine for treatment of asthma over the preceding 12 months, and who had not used any prescribed asthma medications over the preceding 12 months were classified as OTC subjects (n=15). Subjects who had used *both* prescription and OTC medications for the treatment of asthma over the preceding 12 months were classified as PRE/OTC subjects (n=13).

One of the OTC subjects reported using only oral nonprescription ephedrine-containing bronchodilator medications over the 12 months prior to study. All 27 other OTC subjects reported use of epinephrine-containing bronchodilator medications administered via an MDI, with or without oral medications over the 12 months prior to study. The two most common OTC inhaler brands reported were Primatene Mist (n=25) and Bronkaid Mist (n=7) (some subjects used both brands) Five PRE/OTC subjects and six OTC subjects reported use of nonprescription oral ephedrine-containing bronchodilator medications over the 12 months prior to study in addition to their inhaled medications.

Of the 35 subjects who used prescription asthma medication either exclusively or in combination with OTC products (those in either the PRE or PRE/OTC groups), all used prescription β-agonist MDIs and 14 (40%) had used inhaled steroids in the 12 months prior to interview. This included 4 of the 13 PRE/OTC group and 10 of the 22 PRE group (p>0.6).

Statistical Analyses

Diurnal variation in PEFR was calculated for each day as the difference between the maximum morning value and the maximum evening value divided by the maximum value for the entire day. PEFR variability was calculated as the mean of the PEFR diurnal variation×100% for those subjects who carried out PEFR maneuvers on at least 4 days of the 6-day study period. We excluded from the PEFR analysis two subjects (both from the PRE group) who did not record PEFR twice daily for at least 4 days.

We used a standard statistical package in the data analysis (SAS Institute Inc; Cary, NC). Data among the three groups were compared by analysis of variance (normally distributed continuous variables), the Kruskal-Wallis test (income); or the Mantel-Haenszel χ^2 test for trend (dichotomous variables). We used multiple logistic regression to estimate the associations among gender, access to a health-care provider, annual household income, subject perception of asthma severity, and steroid use with the use of nonprescription asthma medications. We carried out these estimations for two models. The first model included exclusive PRE and exclusive OTC subjects, with the dependent variable OTC medication use. The second model included those subjects who used both prescription and nonprescription asthma medications (PRE/OTC) or exclusive PRE users. In the second model, the dependent variable was again nonprescription asthma medication use. The independent variables were the same in both models. To assess the added explanatory power of covariates, we also tested the changes in model χ^2 of the logistic regression with and without these additional variables.

RESULTS

Demographic Characteristics

As shown in Table 1, nonprescription medication use was more common among male subjects than among female subjects (p=0.008, χ^2 test for trend). There was greater nonprescription medication use among persons who did not have a primary caregiver for asthma management, although this difference was of borderline statistical significance (p=0.10).

Table 1—*Demographics and Subject Characteristics

Subject Characteristics	OTC (n=15)	PRE/OTC (n=13)	PRE (n=22)	p Value
Age, yr, mean±SD	33.3±9.3	33.7±8.2	34.7±8.4	>0.8
Female gender, No. (%)	6 (40)	5 (38)	18 (82)	0.008
White non-Hispanic, No. (%)	10 (67)	5 (38)	15 (68)	>0.7
Currently employed, No. (%)	8 (53)	6 (46)	12 (55)	>0.9
Currently insured for health care, No. (%)	9 (60)	6 (46)	17 (77)	0.23
Age of first asthma "attack," yr, mean±SD	12.4±12.2	8.9±11.6	11.5±9.5	>0.6
Age, yr, asthma initially physician diagnosed, mean±SD†	13.3±11.8	13.0±13.7	13.6±11.7	>0.9
Annual family income in thousands of dollars, median [interquartile range]‡	15 [7.5-35]	15 [7.5-25]	20 [15-62.5]	0.23
Have a primary caregiver, No. (%)	7 (47)	6 (46)	16 (73)	0.10
Ever smokers, No. (%)	5 (33)	4 (31)	8 (36)	>0.8

*OTC=users of OTC bronchodilators exclusively over the 12 months prior to study; PRE/OTC=users of both prescription and OTC bronchodilators over the 12 months prior to study; PRE=users of prescription bronchodilators exclusively over the 12 months prior to study; ever smoker=smoked ≥100 cigarettes in entire life.

†One subject each in the OTC and PRE/OTC groups did not report an MD diagnosis.

‡Data not available for two subjects.

Reanalyzed as a dichotomous comparison between PRE subjects and all subjects reporting nonprescription medication use over the prior 12 months (*ie*, PRE [n=22] vs combined OTC and PRE/OTC [n=28]), access to a primary caregiver was more strongly associated with subjects reporting exclusive use of prescription asthma medications: 16 (73%) of PRE subjects reported access to a primary caregiver compared with 13 (46%) of the combined OTC and PRE/OTC subjects (p=0.06).

There was no statistically significant difference in annual household income among the three groups (Table 1). Reanalysis in a dichotomous comparison did not appreciably strengthen the association. There were also no statistically significant differences in age, ethnicity, employment status, insurance status, smoking status, or age of asthma onset among the groups.

Spirometry and PEFR

Pulmonary function data are shown in Table 2. The mean percent predicted values for FEV_1, FVC, and the FEV_1/FVC were within normal range for all groups and were quite similar among the three groups. Mean postbronchodilator improvement in FEV_1 as a percentage of baseline was greater than 10% in all groups and was not statistically different among the groups. In a dichotomous comparison between OTC and PRE/OTC subjects combined (any nonprescription medication use) vs PRE subjects, there was a greater proportion of nonprescription medication users with >10% improvement in FEV_1 postbronchodilator (18/28; 64%) compared with PRE subjects (8/22; 36%), but this was of borderline significance (p=0.09).

PEFR variability was assessed for a total of 48 subjects. Forty-two subjects completed 6 days, 3 subjects completed 5 days, and 3 subjects completed 4 days of PEFR measurements. PEFR variability did not differ meaningfully among the three groups (Table 2).

Health-Care Utilization and Subject Perception of Illness

None of the 15 OTC subjects reported ever having received either oral or IV corticosteroids for the treatment of asthma (Table 3). In contrast, 7 (54%) PRE/OTC subjects and 11 (50%) PRE subjects had at some time been treated with systemic corticosteroids (p=0.004). A history of having been hospitalized for asthma was less common among OTC subjects, although it was of borderline statistical significance (p=0.06), while the proportions reporting any emergency department asthma visits were similar.

There was no statistical difference in subject reported use of nontraditional asthma therapies among the three groups. There was also no statistical difference in subject reported sense of fatalism about their asthma, or in their belief that they would be able to anticipate an asthma decompensation (Table 3).

As shown in Table 3, OTC and PRE/OTC subjects rated their asthma as less severe than the PRE subjects (p=0.02). We further analyzed perceived asthma severity in relation to nonprescription medication by comparing the differences in the postbronchodilator improvement in FEV_1 between those subjects who characterized their asthma as mild vs those who characterized their asthma as moderate to severe. Among PRE subjects, there was a marked difference in mean (±SD) postbronchodilator improvement in FEV_1 among the 6 subjects who characterized their asthma as mild (5.6%±6.2%) and the 16 subjects who characterized their asthma as moderate or severe (18.4%±22.8%) (p=0.05). In contrast, among those subjects who reported exclusive nonprescription medication use, there was a greater change in FEV_1 postbronchodilator among the 10 subjects who characterized their asthma as mild (19.2%±16.8%) compared to those who characterized their asthma as moderate to severe (8.2%±12.6%), although this difference was not statistically significant (p=0.2; among the mixed group, the difference was less pronounced (15.8±3.4 vs 21.2±16.1, p>0.4).

Table 2—*Pulmonary Function*

Pulmonary Function Measure	OTC (n=15)	PRE/OTC (n=13)	PRE (n=22)	p Value
FEV_1, % predicted, mean±SD	89.9±20.0	86.3±19.0	91.5±26.4	>0.8
FVC, % predicted, mean±SD	100.3±15.8	100.0±12.8	98.9±17 4	>0.9
FEV_1/FVC, %±SD	72.9±14.2	69.8±13.3	74.0±15 4	0.7
Postbronchodilator change in FEV_1 as % of baseline, mean±SD	+15.5±16 0	+18 8±11.9	+10.4±20 4	>0.8
PEFR variability, mean %±SD*	9.9±5.6	8.7±4.8	10.0±5.2	>0.7

*Data missing for two PRE subjects.

Table 3—*Subject-Perceived Asthma Severity and Health-Care Utilization*

Descriptor	OTC (n=15)	PRE/OTC (n=13)	PRE (n=22)	p Value
Ever visited an ED* for asthma, No. (%)	8 (53)	9 (69)	14 (64)	>0.5
Ever been hospitalized for asthma, No. (%)	1 (7)	5 (38)	8 (36)	0.06
Have ever received IV or oral corticosteroids for asthma, No. (%)	0 (0)	7 (54)	11 (50)	0.004
Subject perceived asthma severity=moderate or severe, No. (%)	5 (33)	7 (54)	16 (73)	0.02
Fatalistic attitude,† No. (%)	5 (33)	6 (46)	10 (45)	>0.4
Anticipate decompensation,‡ No. (%)	1 (73)	8 (62)	9 (86)	0.3
Have ever used nontraditional therapy for asthma,§ No. (%)	8 (53)	4 (31)	4 (64)	>0.4

*ED=emergency department.
†Subjects who agree or strongly agree with the statement, "It seems as though fate and other factors beyond my control affect my asthma."
‡Subjects who agree or strongly agree with the statement, "Usually, I can tell when my asthma is going to get worse."
§Nontraditional therapy=herbs or caffeine-containing coffee or tea to treat asthma.

Multiple Logistic Regression Analysis

We carried out multiple logistic regression analysis in order to estimate the association between demographic and illness characteristics, analyzed together, in relation to nonprescription asthma medication use. The predictive model included the following: gender; annual household income stratified by quartile; access to primary caregiver for asthma management; and subject assessment of illness severity. We chose these variables because of their associations with OTC and PRE use in the univariate analyses presented previously (Tables 1 and 3).

We tested this predictive model restricting the analysis to OCT and PRE subjects only (n=37) with the dependent variable exclusive nonprescription medication use (model one) or restricting the analysis to mixed PRE/OTC vs PRE alone (model two, n=35) (Table 4). In both of these multiple logistic regression analyses, there was a statistically significant association between male gender and nonprescription medication use even taking into account the other covariates studied. The odds ratio (OR) and confidence interval (CI) for exclusive nonprescription medication use associated with male gender was OR of 8.8 (95% CI, 1.3 to 61), while for mixed nonprescription medication use, it was similar: OR, 9.7 (95% CI, 1.1 to 83). We also reanalyzed model one excluding the two subjects with assigned income values. The gender association was unaffected (OR, 8.3; 95% CI, 1.7 to 42).

To assess whether demographic and illness characteristics, taken together, provided additional explanatory power in predicting any nonprescription medication use, we calculated the difference in model χ^2 of logistic regression model estimated for gender alone. For exclusive nonprescription medication use, the model χ^2 difference with the additional variables compared to gender alone was 11.3 (5 *df*, $p<0.05$), consistent with statistically significant added explanatory power; for mixed use, the χ^2 difference of 7.45 was not as great ($0.10<p<0.20$).

Discussion

Our study suggests a "profile" of the person with asthma who is more likely to self-medicate asthma with nonprescription bronchodilators. The picture that emerges is that of a man who views his asthma as mild, whether or not the degree of reversible airflow obstruction supports that self-assessment. The association with male gender in particular was powerful and is consistent with the findings of a recent Australian study.[19]

To our knowledge, there are no clinical studies supporting the treatment of asthma with inhaled epinephrine in preference to β_2-selective agents. The undersupervised use of oral preparations con-

Table 4—*Risk Factors Associated With OTC Bronchodilator Use**

Risk Factor	Model 1 Exclusive OTC (vs PRE Use Only) OR, 95% CI (n=37)	Model 2 PRE/OTC Use (vs PRE Use Only) OR, 95% CI (n=35)
Male gender	8.9† [1.3-61]	9.7† [1.1-83]
Income		
Highest quartile (referent)	1.0 ---	1.0 ---
Lowest quartile	2.6 [0.2-33]	7.8 [0 4-154]
25-50% quartile	1.8 [0.2-18]	3.1 [0 2-58]
50-75% quartile	1.9 [0.2-23]	22.5† [1.1-466]
Lacking primary caregiver for management of asthma	1.1 [0.6-8]	1.6 [0 2-11]
Self-assessed severity		
Moderate-severe (referent)	1.0 ---	1.0 ---
Mild	7.5 [1.0-57]	1.6 [0.2-10]

*Model one compares exclusive OTC users to exclusive prescription users and *excludes* those in the PRE/OTC group (n=13). Model two compares mixed OTC users (PRE/OTC) with exclusive prescription users and *excludes* those in the OTC group (n=15).
†$p<0.05$.

taining theophylline or ephedrine may carry additional risks of adverse effect. Serious acute and chronic toxic reactions due to nonprescription oral and inhaled bronchodilator medication use, although reported infrequently, do occur.[1-8] Additionally, nonprescription asthma medication use has been linked with underutilization of inhaled corticosteroids.[17,18] We did not study these adverse outcomes in our investigation. Our data do suggest that men who self-assess their disease as "mild" could be at greater risk for these potential outcomes because they are the most likely to self-treat with OTC asthma medications.

The objective physiologic measures of asthma that we analyzed, including severity of airflow obstruction as measured by FEV_1, airflow variability over the course of a week as measured by PEFR, and mean reversibility of airflow obstruction postbronchodilator, did not differ meaningfully by nonprescription medication use. Although these findings argue against mild asthma severity *per se* as being the predominant factor explaining self-medication with nonprescription bronchodilators, prior steroid use was indeed negatively associated with exclusive nonprescription medication use. The greater proportion of those ever hospitalized for asthma among subjects who did not exclusively use asthma OTC may also be a marker of greater severity. Of course, this could reflect variable access to health care.

Importantly, among the nonprescription medication users, we observed no association between an objective measure of airway responsiveness (postbronchodilator change in FEV_1) and subjects' assessment of their own asthma severity. In contrast, the expected association between degree of airflow obstruction reversibility postbronchodilator and self-assessed illness severity (*ie,* greater reversibility of airflow obstruction associated with subject-assessed more severe asthma) was indeed manifest by the exclusive prescription medication users that we studied. This finding is consistent with the concept that dyspnea, or the perception of respiratory impairment, is not necessarily linked with objective measures of functional impairment.[23] That is, self-assessment of asthma severity may not be "on target," especially among individuals who self-medicate their illness with nonprescription bronchodilators. These findings are also consistent with the observation that OTC bronchodilator users perceive less disability from asthma than did prescription bronchodilator users, but they are no different from the prescription users with respect to objective measures of disease severity.[17]

We recognize that there are important limitations to this study. The potential for selection bias is very real and our findings may not be generalizable to all adults with asthma. For example, our study population was derived from individuals responding to newspaper advertisements written in English. Not surprisingly, all of our subjects were both literate and English speaking. For this reason, our findings may not extend to individuals with other demographic profiles. We could not realistically employ the sampling strategy used in prior Australian studies of nonprescription MDIs (which were nevertheless β-selective), where dispensing pharmacies and collaborating pharmacists were key to subject recruitment.[17,18] Nevertheless, among the individuals we did study, we found important differences between prescription and nonprescription medication users, despite the fact that they were all recruited by public advertisement. We would not expect these differences to be attributable solely to selection bias within the larger study group itself.

As with many clinical asthma studies, another potential limitation to our investigation is imprecision in objectively assessing asthma severity. Asthma is, by definition, characterized by episodic exacerbations, typically of variable severity and is, therefore, not easily staged. Illness severity is, however, relevant to any discussion regarding the appropriateness of asthma self-medication with bronchodilators. It is a particularly important assessment to make in studying persons with asthma who may not have access to anti-inflammatory medications. Our objective measures of airflow included both a one-time assessment of pulmonary function and peak flow variability over time, albeit a limited period. Importantly, however, the measures were similar among the three groups defined by medication use. This argues against current physiologic impairment being the principal predictor of asthma self-medication. This, in turn, is relevant because, while it is conceivable that self-medication strategies with nonprescription bronchodilators might be safe for the mildest forms of asthma, standard-of-care for moderate and severe asthma includes the use of anti-inflammatory regimens available only by prescription. In summary, while acknowledging that there are inherent difficulties in characterizing asthma severity, our findings suggest that asthma OTC medication use is not restricted to persons with only the mildest forms of asthma. Particularly among those who tend to mix prescription and OTC pharmaceuticals, asthma severity (gauged by hospitalization, past systemic corticosteroid use, and recent inhaled steroid use) appears to be at least as great as that among exclusive prescription medication users. Finally, our sample size was relatively small. We took this into account by including predictors (income and access to care) in our multiple logistic model that did vary by medica-

tion use even if this variability was not statistically significant at the 0.05 level. Moreover, while the small sample "n" we studied increases the chance for beta error (failure to reject the null hypothesis despite a real difference), it should not lead to inappropriate rejection of the null hypothesis (alpha error). The significant findings we do report are not attributable to the small study "n."

In conclusion, characterizing nonprescription asthma medication users is important because they may be at increased risk of preventable morbidity. To our knowledge, this study is the first in the United States addressing this question. Outreach programs designed to improve knowledge about asthma and specifically intended to discourage inappropriate reliance on nonspecific β-receptor agonist therapy may wish to target men with self-assessed "mild" illness.

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Table 3. Frequencies of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003

Selected characteristic	All persons 18 years of age and over	Selected respiratory conditions[1]					
		Emphysema	Asthma		Hay fever	Sinusitis	Chronic bronchitis
			Ever	Still			
	Number in thousands[2]						
Total[3]	213,042	3,115	20,697	13,623	18,356	29,673	8,560
Sex							
Male	102,298	1,701	8,253	4,665	7,880	10,225	2,741
Female	110,744	1,414	12,444	8,958	10,476	19,447	5,820
Age							
18–44 years	110,538	155	11,204	6,972	9,407	13,183	3,254
45–64 years	68,248	1,261	6,722	4,678	6,710	11,755	3,311
65–74 years	18,097	928	1,602	1,129	1,381	2,776	1,131
75 years and over	16,159	771	1,169	844	858	1,958	865
Race							
1 race[4]	210,869	3,086	20,342	13,393	18,091	29,392	8,423
White	177,830	2,854	17,127	11,348	15,838	25,355	7,365
Black or African American	24,111	194	2,610	1,765	1,654	3,421	910
American Indian or Alaska Native	1,285	*14	161	109	112	177	*72
Asian	7,361	*24	436	172	469	427	*77
Native Hawaiian or other Pacific Islander	282	–	*8	–	*17	*12	–
2 or more races[5]	2,173	*29	354	230	265	280	137
Black or African American, white	239	*2	*38	*17	*32	*15	*20
American Indian or Alaska Native, white	953	*23	165	125	112	174	*70
Hispanic or Latino origin[6] and race							
Hispanic or Latino	26,272	80	1,904	1,207	1,529	2,030	604
Mexican or Mexican American	16,661	*50	926	588	893	1,122	327
Not Hispanic or Latino	186,770	3,035	18,793	12,415	16,826	27,642	7,957
White, single race	153,032	2,778	15,404	10,265	14,436	23,476	6,791
Black or African American, single race	23,492	191	2,524	1,701	1,612	3,349	903
Education[7]							
Less than a high school diploma	29,617	947	3,019	2,220	1,842	3,540	1,616
High school diploma or GED[8]	54,153	1,123	4,532	3,085	3,581	7,218	2,293
Some college	50,424	673	5,283	3,488	5,680	9,042	2,389
Bachelor's degree or higher	48,414	311	4,288	2,646	5,707	7,440	1,323
Family income[9]							
Less than $20,000	38,818	1,068	4,669	3,350	2,827	5,241	2,477
$20,000 or more	159,081	1,893	14,928	9,545	14,424	22,493	5,600
$20,000–$34,999	29,406	731	3,135	2,117	2,162	4,245	1,538
$35,000–$54,999	32,322	428	3,227	2,120	2,818	5,055	1,323
$55,000–$74,999	23,028	191	2,063	1,302	2,173	3,633	592
$75,000 or more	42,286	230	3,944	2,402	4,646	6,144	1,111
Poverty status[10]							
Poor	18,137	426	2,328	1,691	1,194	2,400	1,223
Near poor	27,545	672	3,121	2,153	2,340	3,894	1,577
Not poor	111,175	1,385	10,640	6,773	10,534	16,974	3,846
Health insurance coverage[11]							
Under age 65 years:							
Private	125,722	754	11,785	7,485	12,189	18,801	4,096
Medicaid	11,911	288	2,062	1,592	993	1,782	1,052
Other	5,709	231	634	474	574	954	363
Uninsured	34,519	143	3,369	2,044	2,338	3,332	1,032
Age 65 years and over:							
Private	21,521	934	1,648	1,156	1,479	3,098	1,220
Medicaid and Medicare	2,065	227	370	322	161	357	242
Medicare only	7,902	352	573	380	426	992	416
Other	2,383	176	164	108	165	260	117
Uninsured	312	*10	*16	*7	*5	*24	–

See footnotes at end of table.

Table 3. Frequencies of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003—Con.

Selected characteristic	All persons 18 years of age and over	Selected respiratory conditions[1]					
		Emphysema	Asthma		Hay fever	Sinusitis	Chronic bronchitis
			Ever	Still			
	Number in thousands[2]						
Marital status							
Married	123,049	1,797	10,634	6,887	11,050	17,865	4,463
Widowed	13,906	535	1,337	1,044	988	2,060	909
Divorced or separated	22,400	542	2,506	1,802	2,327	3,934	1,308
Never married	41,346	134	4,798	2,917	3,005	4,297	1,329
Living with a partner	11,309	103	1,353	928	920	1,447	525
Place of residence[12]							
Large MSA	100,217	1,114	9,196	6,063	8,714	12,928	3,327
Small MSA	69,903	1,040	7,088	4,624	5,923	9,936	3,059
Not in MSA	42,922	961	4,413	2,935	3,719	6,808	2,174
Region							
Northeast	40,954	577	4,322	2,855	3,779	5,380	1,485
Midwest	52,206	791	5,414	3,595	4,197	7,352	2,065
South	77,592	1,311	6,640	4,422	5,812	12,596	3,585
West	42,289	435	4,320	2,751	4,568	4,345	1,426
Sex and ethnicity							
Hispanic or Latino, male	13,447	*50	797	428	733	709	213
Hispanic or Latina, female	12,825	*30	1,107	779	796	1,322	391
Not Hispanic or Latino:							
White, single race, male	73,466	1,514	6,066	3,460	6,229	8,392	2,190
White, single race, female	79,566	1,263	9,338	6,805	8,207	15,064	4,602
Black or African American, single race, male	10,454	96	956	570	599	877	266
Black or African American, single race, female	13,038	*95	1,568	1,131	1,013	2,472	636

* Data preceded by an asterisk have a relative standard error of greater than 30%, and should be used with caution as they do not meet the standard of reliability or precision.

– Quantity zero.

[1]Respondents were asked in two separate questions if they had ever been told by a doctor or other health professional that they had emphysema or asthma. Respondents who had been told they had asthma were asked if they still had asthma. Respondents were asked in three separate questions if they had been told by a doctor or other health professional in the past 12 months that they had hay fever, sinusitis, or bronchitis. A person may be represented in more than one column.

[2]Unknowns for the columns are not included in the frequencies (see "Appendix I") but they are included in the "All persons 18 years of age and over" column. The numbers in this table are rounded.

[3]Total includes other races not shown separately and persons with unknown education, family income, poverty status, health insurance, and marital status characteristics.

[4]In accordance with the 1997 Standards for Federal data on race and Hispanic or Latino origin (see "Appendix II"), the category "1 race" refers to persons who indicated only a single race group. Persons who indicated a single race other than the groups shown are included in the total for "1 race," but not shown separately due to small sample sizes. Therefore, the frequencies for the category "1 race" will be greater than the sum of the frequencies for the specific groups shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races. The tables in this report use the complete new Office of Management and Budget race and Hispanic origin terms, and the text uses shorter versions of these terms for conciseness. For example, the category "1 race, black or African American" in the tables is referred to as "black persons" in the text.

[5]The category "2 or more races" refers to all persons who indicated more than one race group. Only two combinations of multiple race groups are shown due to small sample sizes for other combinations. Therefore, the frequencies for the category "2 or more races" will be greater than the sum of the frequencies for the specific combinations shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races.

[6]Persons of Hispanic or Latino origin may be of any race or combination of races. Similarly, the category "Not Hispanic or Latino" refers to all persons who are not of Hispanic or Latino origin, regardless of race.

[7]Education is shown only for persons aged 25 years and over.

[8]GED is General Educational Development high school equivalency diploma.

[9]The categories "Less than $20,000" and "$20,000 or more" include both persons reporting dollar amounts and persons reporting only that their incomes were within one of these two categories (see "Appendix I"). The indented categories include only those persons who reported dollar amounts.

[10]Poverty status is based on family income and family size using the U.S. Census Bureau's poverty thresholds for the previous calendar year. "Poor" persons are defined as below the poverty threshold. "Near poor" persons have incomes of 100% to less than 200% of the poverty threshold. "Not poor" persons have incomes that are 200% of the poverty threshold or greater.

[11]Classification of health insurance coverage is based on a hierarchy of mutually exclusive categories. Persons with more than one type of health insurance were assigned to the first appropriate category in the hierarchy. Persons under age 65 years and those age 65 years and over were classified separately due to the prominence of Medicare coverage in the older population. The category "private" includes persons who had any type of private coverage either alone or in combination with other coverage. For example, for persons age 65 years and over, "private" includes persons with only private coverage or private coverage in combination with Medicare. The category "Uninsured" includes persons who had no coverage as well as those who had only Indian Health Service coverage or had only a private plan that paid for one type of service such as accidents or dental care (see "Appendix II").

[12]MSA is metropolitan statistical area. Large MSAs have a population size of 1,000,000 or more; small MSAs have a population size of less than 1,000,000. "Not in MSA" consists of persons not living in a metropolitan statistical area.

DATA SOURCE: National Health Interview Survey, 2003.

Table 4. Age-adjusted percentages (with standard errors) of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003

Selected characteristic	Selected respiratory conditions[1]					
		Asthma				
	Emphysema	Ever	Still	Hay fever	Sinusitis	Chronic bronchitis
	Percent[2] (standard error)					
Total[3] (age-adjusted)	1.5 (0.08)	9.7 (0.19)	6.4 (0.16)	8.6 (0.19)	13.9 (0.26)	4.0 (0.13)
Total[3] (crude)	1.5 (0.08)	9.7 (0.19)	6.4 (0.16)	8.6 (0.19)	14.0 (0.26)	4.0 (0.13)
Sex						
Male	1.8 (0.13)	8.0 (0.26)	4.6 (0.21)	7.6 (0.27)	10.0 (0.33)	2.7 (0.16)
Female	1.2 (0.09)	11.3 (0.28)	8.1 (0.25)	9.5 (0.25)	17.5 (0.37)	5.2 (0.21)
Age[4]						
18–44 years	0.1 (0.03)	10.1 (0.28)	6.3 (0.23)	8.5 (0.28)	11.9 (0.34)	2.9 (0.17)
45–64 years	1.9 (0.17)	9.9 (0.34)	6.9 (0.28)	9.8 (0.35)	17.3 (0.46)	4.9 (0.23)
65–74 years	5.1 (0.46)	8.9 (0.58)	6.2 (0.51)	7.6 (0.57)	15.4 (0.85)	6.3 (0.52)
75 years and over	4.8 (0.48)	7.3 (0.59)	5.2 (0.48)	5.3 (0.48)	12.2 (0.73)	5.4 (0.49)
Race						
1 race[5]	1.5 (0.08)	9.6 (0.19)	6.3 (0.16)	8.5 (0.19)	13.9 (0.26)	4.0 (0.13)
White	1.6 (0.09)	9.6 (0.21)	6.4 (0.18)	8.9 (0.22)	14.1 (0.28)	4.1 (0.15)
Black or African American	1.0 (0.19)	10.7 (0.57)	7.2 (0.44)	6.8 (0.46)	14.3 (0.64)	3.9 (0.34)
American Indian or Alaska Native	*1.1 (0.84)	12.4 (2.41)	8.0 (1.75)	9.4 (2.43)	15.1 (2.83)	5.2 (1.43)
Asian	*0.5 (0.27)	6.4 (0.95)	2.7 (0.57)	6.5 (0.88)	5.5 (0.76)	*1.4 (0.45)
Native Hawaiian or other Pacific Islander	–	*1.9 (1.92)	–	*4.1 (2.58)	*2.8 (2.18)	–
2 or more races[6]	*1.4 (0.66)	15.7 (2.13)	10.4 (1.83)	12.2 (2.08)	14.5 (2.12)	6.7 (1.49)
Black or African American, white	*1.7 (1.72)	*16.1 (6.68)	*9.9 (5.69)	*15.5 (6.21)	*9.4 (5.48)	*14.4 (5.67)
American Indian or Alaska Native, white	*2.5 (1.28)	17.0 (3.47)	13.2 (3.22)	12.0 (2.84)	20.8 (3.32)	*8.1 (2.62)
Hispanic or Latino origin[7] and race						
Hispanic or Latino	0.6 (0.16)	7.5 (0.47)	4.8 (0.36)	6.3 (0.44)	8.5 (0.53)	2.8 (0.34)
Mexican or Mexican American	*0.8 (0.29)	6.0 (0.60)	3.8 (0.46)	5.6 (0.55)	7.8 (0.69)	2.8 (0.53)
Not Hispanic or Latino	1.6 (0.08)	10.1 (0.21)	6.7 (0.18)	9.0 (0.21)	14.7 (0.29)	4.2 (0.15)
White, single race	1.6 (0.09)	10.2 (0.24)	6.7 (0.20)	9.5 (0.24)	15.2 (0.32)	4.3 (0.17)
Black or African American, single race	1.0 (0.19)	10.6 (0.57)	7.1 (0.44)	6.8 (0.47)	14.3 (0.65)	4.0 (0.35)
Education[8]						
Less than a high school diploma	2.7 (0.26)	10.1 (0.52)	7.4 (0.46)	6.3 (0.43)	11.6 (0.59)	5.1 (0.38)
High school diploma or GED[9]	1.9 (0.17)	8.4 (0.35)	5.7 (0.30)	6.6 (0.30)	13.1 (0.46)	4.1 (0.26)
Some college	1.5 (0.16)	10.3 (0.38)	6.8 (0.33)	11.0 (0.43)	17.8 (0.53)	4.7 (0.28)
Bachelor's degree or higher	0.9 (0.14)	8.7 (0.38)	5.4 (0.30)	11.6 (0.44)	15.2 (0.52)	2.9 (0.23)
Family income[10]						
Less than $20,000	2.7 (0.24)	12.4 (0.45)	8.9 (0.38)	7.4 (0.39)	13.6 (0.52)	6.4 (0.35)
$20,000 or more	1.3 (0.09)	9.3 (0.23)	6.0 (0.19)	8.9 (0.23)	13.9 (0.29)	3.6 (0.15)
$20,000–$34,999	2.3 (0.26)	10.8 (0.51)	7.3 (0.42)	7.5 (0.46)	14.7 (0.62)	5.2 (0.37)
$35,000–$54,999	1.5 (0.22)	9.9 (0.51)	6.5 (0.42)	8.5 (0.45)	15.6 (0.63)	4.2 (0.35)
$55,000–$74,999	1.1 (0.24)	9.0 (0.65)	5.7 (0.54)	8.9 (0.58)	15.4 (0.82)	2.9 (0.45)
$75,000 or more	0.8 (0.22)	9.0 (0.52)	5.5 (0.43)	10.6 (0.53)	13.8 (0.61)	2.7 (0.29)
Poverty status[11]						
Poor	2.9 (0.40)	13.5 (0.72)	9.8 (0.59)	6.7 (0.53)	13.8 (0.75)	7.4 (0.56)
Near poor	2.6 (0.30)	11.5 (0.58)	8.0 (0.50)	8.7 (0.53)	14.4 (0.65)	5.8 (0.40)
Not poor	1.4 (0.12)	9.5 (0.28)	6.1 (0.23)	9.2 (0.27)	15.0 (0.34)	3.5 (0.18)
Health insurance coverage[12]						
Under age 65 years:						
Private	0.5 (0.06)	9.4 (0.26)	6.0 (0.21)	9.7 (0.28)	14.7 (0.34)	3.2 (0.17)
Medicaid	2.7 (0.47)	17.8 (1.01)	13.7 (0.91)	8.5 (0.65)	15.3 (0.98)	9.2 (0.72)
Other	2.6 (0.53)	11.0 (1.24)	7.8 (1.14)	9.4 (1.29)	16.0 (1.61)	5.1 (0.87)
Uninsured	0.5 (0.14)	9.8 (0.53)	6.0 (0.42)	6.8 (0.43)	10.2 (0.53)	3.1 (0.29)
Age 65 years and over:						
Private	4.3 (0.40)	7.7 (0.52)	5.4 (0.45)	6.9 (0.53)	14.4 (0.75)	5.7 (0.43)
Medicaid and Medicare	11.3 (1.90)	18.1 (2.14)	15.8 (2.12)	7.9 (1.44)	17.5 (2.11)	11.8 (2.09)
Medicare only	4.5 (0.72)	7.3 (0.81)	4.8 (0.61)	5.4 (0.66)	12.6 (1.16)	5.3 (0.74)
Other	7.5 (1.50)	6.7 (1.21)	4.5 (1.01)	6.9 (1.37)	10.9 (1.75)	4.9 (1.22)
Uninsured	*2.7 (1.58)	*5.4 (3.17)	*1.8 (1.79)	*1.3 (1.04)	*7.1 (3.60)	–

See footnotes at end of table.

Table 4. Age-adjusted percentages (with standard errors) of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003—Con.

Selected characteristic	Selected respiratory conditions[1]					
		Asthma				
	Emphysema	Ever	Still	Hay fever	Sinusitis	Chronic bronchitis
	Percent[2] (standard error)					
Marital status						
Married	1.4 (0.11)	8.6 (0.26)	5.5 (0.22)	8.9 (0.27)	14.2 (0.35)	3.6 (0.18)
Widowed	1.7 (0.28)	10.0 (1.71)	8.4 (1.67)	8.4 (1.96)	15.8 (2.21)	5.8 (1.13)
Divorced or separated	2.4 (0.26)	11.0 (0.53)	7.8 (0.46)	10.1 (0.54)	16.7 (0.70)	5.7 (0.40)
Never married	1.1 (0.22)	11.1 (0.54)	7.0 (0.42)	7.1 (0.41)	11.8 (0.57)	3.8 (0.36)
Living with a partner	2.3 (0.69)	11.9 (1.20)	8.6 (1.04)	8.9 (1.04)	12.9 (1.12)	5.4 (0.86)
Place of residence[13]						
Large MSA	1.2 (0.11)	9.1 (0.28)	6.0 (0.24)	8.6 (0.28)	12.9 (0.33)	3.4 (0.18)
Small MSA	1.4 (0.13)	10.2 (0.33)	6.6 (0.26)	8.4 (0.36)	14.1 (0.46)	4.3 (0.22)
Not in MSA	2.1 (0.20)	10.3 (0.42)	6.8 (0.39)	8.6 (0.41)	15.7 (0.71)	5.0 (0.37)
Region						
Northeast	1.3 (0.17)	10.7 (0.48)	7.0 (0.39)	9.3 (0.43)	13.2 (0.55)	3.6 (0.29)
Midwest	1.5 (0.16)	10.4 (0.41)	6.9 (0.35)	8.0 (0.38)	14.1 (0.55)	4.0 (0.27)
South	1.7 (0.14)	8.5 (0.30)	5.7 (0.25)	7.4 (0.30)	16.1 (0.48)	4.6 (0.23)
West	1.2 (0.15)	10.2 (0.41)	6.5 (0.36)	10.8 (0.51)	10.4 (0.46)	3.5 (0.27)
Sex and ethnicity						
Hispanic or Latino, male	*0.8 (0.31)	6.0 (0.66)	3.2 (0.48)	5.7 (0.58)	5.9 (0.65)	2.0 (0.40)
Hispanic or Latina, female	*0.3 (0.12)	8.9 (0.69)	6.3 (0.54)	6.8 (0.59)	11.0 (0.75)	3.5 (0.49)
Not Hispanic or Latino:						
White, single race, male	2.0 (0.16)	8.4 (0.32)	4.7 (0.25)	8.4 (0.34)	11.3 (0.40)	3.0 (0.21)
White, single race, female	1.4 (0.11)	11.9 (0.35)	8.6 (0.31)	10.5 (0.32)	18.9 (0.45)	5.6 (0.26)
Black or African American, single race, male	1.3 (0.34)	8.7 (0.85)	5.2 (0.64)	5.7 (0.65)	8.3 (0.82)	2.6 (0.46)
Black or African American, single race, female	*0.8 (0.25)	12.0 (0.78)	8.6 (0.65)	7.7 (0.65)	19.1 (0.98)	5.0 (0.49)

* Data preceded by an asterisk have a relative standard error of greater than 30%, and should be used with caution as they do not meet the standard of reliability or precision.

– Quantity zero.

[1]Respondents were asked in two separate questions if they had ever been told by a doctor or other health professional that they had emphysema or asthma. Respondents who had been told they had asthma were asked if they still had asthma. Respondents were asked in three separate questions if they had been told by a doctor or other health professional in the past 12 months that they had hay fever, sinusitis, or bronchitis. A person may be represented in more than one column.

[2]Unknowns for the columns are not included in the denominators when calculating percents (see "Appendix I"). The percents in this table are rounded.

[3]Total includes other races not shown separately and persons with unknown education, family income, poverty status, health insurance, and marital status characteristics.

[4]Estimates for age groups are not age adjusted.

[5]In accordance with the 1997 Standards for Federal data on race and Hispanic or Latino origin (see "Appendix I"), the category "1 race" refers to persons who indicated only a single race group. Persons who indicated a single race other than the groups shown are included in the total for "1 race" but not shown separately due to small sample sizes. Therefore, the frequencies for the category "1 race" will be greater than the sum of the frequencies for the specific groups shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races. The tables in this report use the complete new OMB race and Hispanic origin terms, and the text uses shorter versions of these terms for conciseness. For example, the category "1 race, black or African American" in the tables is referred to as "black persons" in the text.

[6]The category "2 or more races" refers to all persons who indicated more than one race group. Only two combinations of multiple race groups are shown due to small sample sizes for other combinations. Therefore, the frequencies for the category "2 or more races" will be greater than the sum of the frequencies for the specific combinations shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races.

[7]Persons of Hispanic or Latino origin may be of any race or combination of races. Similarly, the category "Not Hispanic or Latino" refers to all persons who are not of Hispanic or Latino origin, regardless of race.

[8]Education is shown only for persons aged 25 years and over. Estimates are age adjusted to the 2000 U.S. standard population using four age groups: 25–44 years, 45–64 years, 65–74 years, and 75 years and over.

[9]GED is General Educational Development high school equivalency diploma.

[10]The categories "Less than $20,000" and "$20,000 or more" include both persons reporting dollar amounts and persons reporting only that their incomes were within one of these two categories (see "Appendix I"). The indented categories include only those persons who reported dollar amounts.

[11]Poverty status is based on family income and family size using the Census Bureau's poverty thresholds for the previous calendar year. "Poor" persons are defined as below the poverty threshold. "Near poor" persons have incomes of 100% to less than 200% of the poverty threshold. "Not poor" persons have incomes that are 200% of the poverty threshold or greater.

[12]Classification of health insurance coverage is based on a hierarchy of mutually exclusive categories. Persons with more than one type of health insurance were assigned to the first appropriate category in the hierarchy. Persons under age 65 years and those age 65 years and over were classified separately due to the prominence of Medicare coverage in the older population. The category "private" includes persons who had any type of private coverage either alone or in combination with other coverage. For example, for persons age 65 years and over, "private" includes persons with only private coverage or private coverage in combination with Medicare. The category "Uninsured" includes persons who had no coverage as well as those who had only Indian Health Service coverage or had only a private plan that paid for one type of service such as accidents or dental care (see "Appendix I").

[13]MSA is metropolitan statistical area. Large MSAs have a population size of 1,000,000 or more; small MSAs have a population size of less than 1,000,000. "Not in MSA" consists of persons not living in a metropolitan statistical area.

NOTES: Unless otherwise specified, estimates are age adjusted to the 2000 U.S. standard population using four age groups 18–44 years, 45–64 years, 65–74 years, and 75 years and over. For crude percents, refer to table V in "Appendix III."

Data source: National Health Interview Survey, 2003.

Table V. Crude percentages (with standard errors) of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003

Selected characteristic	Selected respiratory conditions[1]					
		Asthma				
	Emphysema	Ever	Still	Hay fever	Sinusitis	Chronic bronchitis
	Percent[2] (standard error)					
Total[3] (crude)	1.5 (0.08)	9.7 (0.19)	6.4 (0.16)	8.6 (0.19)	14.0 (0.26)	4.0 (0.13)
Total[3] (age-adjusted)	1.5 (0.08)	9.7 (0.19)	6.4 (0.16)	8.6 (0.19)	13.9 (0.26)	4.0 (0.13)
Sex						
Male	1.7 (0.12)	8.1 (0.26)	4.6 (0.21)	7.7 (0.27)	10.0 (0.33)	2.7 (0.16)
Female	1.3 (0.10)	11.3 (0.28)	8.1 (0.25)	9.5 (0.25)	17.6 (0.37)	5.3 (0.21)
Age						
18–44 years	0.1 (0.03)	10.1 (0.28)	6.3 (0.23)	8.5 (0.28)	11.9 (0.34)	2.9 (0.17)
45–64 years	1.9 (0.17)	9.9 (0.34)	6.9 (0.28)	9.8 (0.35)	17.3 (0.46)	4.9 (0.23)
65–74 years	5.1 (0.46)	8.9 (0.58)	6.2 (0.51)	7.6 (0.57)	15.4 (0.85)	6.3 (0.52)
75 years and over	4.8 (0.48)	7.3 (0.59)	5.2 (0.48)	5.3 (0.48)	12.2 (0.73)	5.4 (0.49)
Race						
1 race[4]	1.5 (0.08)	9.7 (0.19)	6.4 (0.16)	8.6 (0.19)	14.0 (0.27)	4.0 (0.13)
White	1.6 (0.09)	9.6 (0.21)	6.4 (0.18)	8.9 (0.22)	14.3 (0.29)	4.1 (0.15)
Black or African American	0.8 (0.16)	10.8 (0.58)	7.3 (0.45)	6.9 (0.48)	14.2 (0.66)	3.8 (0.33)
American Indian or Alaska Native	*1.1 (0.82)	12.6 (2.45)	8.4 (1.86)	8.7 (2.35)	13.8 (2.50)	5.6 (1.52)
Asian	*0.3 (0.19)	5.9 (0.88)	2.3 (0.47)	6.4 (0.88)	5.8 (0.82)	*1.0 (0.33)
Native Hawaiian or other Pacific Islander	–	*2.7 (2.77)	–	*6.0 (3.69)	*4.1 (3.13)	–
2 or more races[5]	*1.3 (0.60)	16.3 (2.27)	10.7 (1.96)	12.2 (2.07)	13.0 (1.98)	6.3 (1.43)
Black or African American, white	*1.0 (0.97)	*15.8 (6.28)	*7.5 (4.37)	*13.3 (5.38)	*8.2 (3.94)	*8.3 (4.99)
American Indian or Alaska Native, white	*2.4 (1.27)	17.3 (3.55)	13.1 (3.26)	11.7 (2.83)	18.4 (3.48)	*7.4 (2.45)
Hispanic or Latino origin[6] and race						
Hispanic or Latino	0.3 (0.07)	7.2 (0.45)	4.6 (0.35)	5.8 (0.41)	7.7 (0.46)	2.3 (0.25)
Mexican or Mexican American	*0.3 (0.10)	5.6 (0.53)	3.5 (0.43)	5.4 (0.50)	6.7 (0.54)	2.0 (0.30)
Not Hispanic or Latino	1.6 (0.09)	10.1 (0.21)	6.7 (0.17)	9.0 (0.21)	14.8 (0.29)	4.3 (0.15)
White, single race	1.8 (0.11)	10.1 (0.23)	6.7 (0.20)	9.4 (0.24)	15.4 (0.32)	4.4 (0.17)
Black or African American, single race	0.8 (0.16)	10.8 (0.59)	7.2 (0.45)	6.9 (0.49)	14.3 (0.68)	3.8 (0.34)
Education[7]						
Less than a high school diploma	3.2 (0.30)	10.2 (0.50)	7.5 (0.43)	6.2 (0.40)	12.0 (0.59)	5.5 (0.39)
High school diploma or GED[8]	2.1 (0.19)	8.4 (0.35)	5.7 (0.30)	6.6 (0.30)	13.4 (0.48)	4.2 (0.26)
Some college	1.3 (0.15)	10.5 (0.39)	6.9 (0.34)	11.3 (0.45)	18.0 (0.53)	4.7 (0.29)
Bachelor's degree or higher	0.6 (0.11)	8.9 (0.38)	5.5 (0.30)	11.8 (0.44)	15.4 (0.52)	2.7 (0.21)
Family income[9]						
Less than $20,000	2.8 (0.25)	12.1 (0.42)	8.6 (0.35)	7.3 (0.37)	13.5 (0.51)	6.4 (0.34)
$20,000 or more	1.2 (0.08)	9.4 (0.23)	6.0 (0.19)	9.1 (0.23)	14.2 (0.30)	3.5 (0.15)
$20,000–$34,999	2.5 (0.28)	10.7 (0.50)	7.2 (0.42)	7.4 (0.45)	14.5 (0.61)	5.2 (0.37)
$35,000–$54,999	1.3 (0.20)	10.0 (0.51)	6.6 (0.43)	8.7 (0.47)	15.7 (0.62)	4.1 (0.35)
$55,000–$74,999	0.8 (0.18)	9.0 (0.59)	5.7 (0.46)	9.4 (0.61)	15.8 (0.81)	2.6 (0.35)
$75,000 or more	0.5 (0.13)	9.3 (0.50)	5.7 (0.40)	11.0 (0.51)	14.5 (0.59)	2.6 (0.27)
Poverty status[10]						
Poor	2.4 (0.33)	12.9 (0.68)	9.4 (0.56)	6.6 (0.53)	13.2 (0.72)	6.8 (0.53)
Near poor	2.4 (0.28)	11.3 (0.55)	7.8 (0.47)	8.5 (0.50)	14.2 (0.62)	5.7 (0.40)
Not poor	1.2 (0.10)	9.6 (0.28)	6.1 (0.23)	9.5 (0.28)	15.3 (0.35)	3.5 (0.17)
Health insurance coverage[11]						
Under age 65 years:						
Private	0.6 (0.07)	9.4 (0.26)	6.0 (0.21)	9.7 (0.27)	15.0 (0.35)	3.3 (0.17)
Medicaid	2.4 (0.43)	17.4 (1.00)	13.4 (0.89)	8.3 (0.64)	15.0 (0.97)	6.8 (0.71)
Other	4.0 (0.76)	11.1 (1.14)	8.3 (1.04)	10.1 (1.16)	16.7 (1.41)	6.4 (0.88)
Uninsured	0.4 (0.11)	9.8 (0.53)	5.9 (0.41)	6.8 (0.43)	9.7 (0.51)	3.0 (0.27)
Age 65 years and over:						
Private	4.3 (0.40)	7.7 (0.52)	5.4 (0.46)	6.9 (0.53)	14.4 (0.75)	5.7 (0.43)
Medicaid and Medicare	11.2 (1.90)	18.0 (2.14)	15.6 (2.12)	7.8 (1.44)	17.3 (2.11)	11.8 (2.09)
Medicare only	4.5 (0.72)	7.3 (0.81)	4.8 (0.61)	5.4 (0.66)	12.6 (1.16)	5.3 (0.74)
Other	7.4 (1.45)	6.9 (1.21)	4.5 (1.00)	6.9 (1.37)	10.9 (1.74)	4.9 (1.20)
Uninsured	*3.2 (1.86)	*5.1 (2.96)	*2.1 (2.11)	*1.5 (1.22)	*7.8 (4.10)	–

See footnotes at end of table.

Table V. Crude percentages (with standard errors) of selected respiratory diseases among persons 18 years of age and over, by selected characteristics: United States, 2003—Con.

Selected characteristic	Selected respiratory conditions[1]					
		Asthma				
	Emphysema	Ever	Still	Hay fever	Sinusitis	Chronic bronchitis
	Percent[2] (standard error)					
Marital status						
Married	1.5 (0.11)	8.7 (0.25)	5.6 (0.22)	9.0 (0.27)	14.5 (0.36)	3.6 (0.17)
Widowed	3.9 (0.39)	9.6 (0.59)	7.5 (0.53)	7.1 (0.53)	14.9 (0.80)	6.6 (0.51)
Divorced or separated	2.4 (0.27)	11.2 (0.51)	8.1 (0.44)	10.4 (0.51)	17.6 (0.65)	5.8 (0.38)
Never married	0.3 (0.06)	11.6 (0.50)	7.1 (0.39)	7.3 (0.39)	10.4 (0.48)	3.2 (0.29)
Living with a partner	0.9 (0.25)	12.0 (1.01)	8.2 (0.81)	8.1 (0.79)	12.8 (0.98)	4.6 (0.60)
Place of residence[12]						
Large MSA	1.1 (0.10)	9.2 (0.29)	6.1 (0.24)	8.7 (0.28)	12.9 (0.33)	3.3 (0.18)
Small MSA	1.5 (0.14)	10.2 (0.33)	6.6 (0.26)	8.5 (0.36)	14.2 (0.47)	4.4 (0.23)
Not in MSA	2.2 (0.22)	10.3 (0.41)	6.9 (0.39)	8.7 (0.41)	15.9 (0.72)	5.1 (0.37)
Region						
Northeast	1.4 (0.19)	10.6 (0.47)	7.0 (0.38)	9.2 (0.42)	13.2 (0.54)	3.6 (0.29)
Midwest	1.5 (0.16)	10.4 (0.41)	6.9 (0.35)	8.0 (0.38)	14.1 (0.55)	4.0 (0.27)
South	1.7 (0.14)	8.6 (0.30)	5.7 (0.25)	7.5 (0.30)	16.3 (0.49)	4.6 (0.24)
West	1.0 (0.14)	10.2 (0.41)	6.5 (0.36)	10.8 (0.52)	10.3 (0.46)	3.4 (0.26)
Sex and ethnicity						
Hispanic or Latino, male	*0.4 (0.12)	5.9 (0.63)	3.2 (0.49)	5.5 (0.55)	5.3 (0.57)	1.6 (0.31)
Hispanic or Latina, female	*0.2 (0.09)	8.6 (0.66)	6.1 (0.52)	6.2 (0.55)	10.3 (0.69)	3.0 (0.41)
Not Hispanic or Latino:						
White, single race, male	2.1 (0.17)	8.3 (0.31)	4.7 (0.25)	8.5 (0.34)	11.4 (0.41)	3.0 (0.20)
White, single race, female	1.6 (0.13)	11.8 (0.34)	8.6 (0.30)	10.3 (0.31)	19.0 (0.45)	5.8 (0.26)
Black or African American, single race, male	0.9 (0.23)	9.2 (0.90)	5.4 (0.68)	5.7 (0.68)	8.4 (0.82)	2.6 (0.45)
Black or African American, single race, female	*0.7 (0.23)	12.0 (0.79)	8.7 (0.65)	7.8 (0.66)	19.0 (0.99)	4.9 (0.48)

* Data preceded by an asterisk have a relative standard error of greater than 30% and should be used with caution, as they do not meet the standard of reliability or precision.

– Quantity zero.

[1]Respondents were asked in two separate questions if they had ever been told by a doctor or other health professional that they had emphysema or asthma. Respondents who had been told they had asthma were asked if they still had asthma. Respondents were asked in three separate questions if they had been told by a doctor or other health professional in the past 12 months that they had hay fever, sinusitis, or bronchitis. A person may be represented in more than one column.

[2]Unknowns for the columns are not included in the denominators when calculating percents (see "Appendix I"). The percents in this table are rounded.

[3]Total includes other races not shown separately and persons with unknown education, family income, poverty status, health insurance, and marital status characteristics.

[4]In accordance with the 1997 Standards for Federal data on race and Hispanic or Latino origin (see "Appendix II"), the category "1 race" refers to persons who indicated only a single race group. Persons who indicated a single race other than the groups shown are included in the total for "1 race" but are not shown separately due to small sample sizes. Therefore, the frequencies for the category "1 race" will be greater than the sum of the frequencies for the specific groups shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races. The tables in this report use the complete new Office of Management and Budget race and Hispanic origin terms, and the text uses shorter versions of these terms for conciseness. For example, the category "1 race, black or African American" in the tables is referred to as "black persons" in the text.

[5]The category "2 or more races" refers to all persons who indicated more than one race group. Only two combinations of multiple race groups are shown due to small sample sizes for other combinations. Therefore, the frequencies for the category "2 or more races" will be greater than the sum of the frequencies for the specific combinations shown separately. Persons of Hispanic or Latino origin may be of any race or combination of races.

[6]Persons of Hispanic or Latino origin may be of any race or combination of races. Similarly, the category "Not Hispanic or Latino" refers to all persons who are not of Hispanic or Latino origin, regardless of race.

[7]Education is shown only for persons aged 25 years and over.

[8]GED is General Educational Development high school equivalency diploma.

[9]The categories "Less than $20,000" and "$20,000 or more" include both persons reporting dollar amounts and persons reporting only that their incomes were within one of these two categories (see "Appendix I"). The indented categories include only those persons who reported dollar amounts.

[10]Poverty status is based on family income and family size using the U.S. Census Bureau's poverty thresholds for the previous calendar year. "Poor" persons are defined as below the poverty threshold. "Near poor" persons have incomes of 100% to less than 200% of the poverty threshold. "Not poor" persons have incomes that are 200% of the poverty threshold or greater.

[11]Classification of health insurance coverage is based on a hierarchy of mutually exclusive categories. Persons with more than one type of health insurance were assigned to the first appropriate category in the hierarchy. Persons under age 65 years and those age 65 years and over were classified separately due to the prominence of Medicare coverage in the older population. The category "private" includes persons who had any type of private coverage either alone or in combination with other coverage. For example, for persons age 65 years and over, "private" includes persons with only private coverage or private coverage in combination with Medicare. The category "Uninsured" includes persons who had no coverage as well as those who had only Indian Health Service coverage or had only a private plan that paid for one type of service such as accidents or dental care (see "Appendix II").

[12]MSA is metropolitan statistical area. Large MSAs have a population size of 1,000,000 or more; small MSAs have a population size of less than 1,000,000. "Not in MSA" consists of persons not living in a metropolitan statistical area.

NOTE: For age-adjusted percents, refer to table 4.

DATA SOURCE: National Health Interview Survey, 2003.

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ABUSE OF INTRAVENOUS PRIMATENE MIST.
U.G. Mason, M D.* and E. Siegal, M.D., Denver, CO

Primatene Mist is an over-the-counter inhaled bronchodilator that is used by asthmatics to control their respiratory symptoms. We report a case of an asthmatic overdosing on Primatene by intravenously injecting the contents of a canister

A 34 year old asthmatic with a history of polysubstance abuse came to the emergency room after he complained of chest pain following intravenous injection of Primatene Mist The event was precipitated by the death of his son and separation from his spouse. He complained of chest pain that radiated to his right shoulder and arm Vital signs were pulse 115, B/P 150/90, respirations 14 without wheezes; an EKG showed sinus tachycardia with a left bundle branch block and no ectopy. In the emergency room he received sublingual nitroglycerin and the chest pain improved. His muscle enzymes were elevated with a normal cardiac fraction; electrolytes and chest x-ray were normal. After two days of sinus rhythm, he was transferred to psychiatry

This case represents a dramatic example of the physical consequences of abusing intravenous epinephrine Tremor, tachycardia and palpitations are common; hypokalemia is a more serious side effect. In an asthmatic with a history of substance abuse and depression, awareness of the possibility of an overdose of epinephrine may prevent more serious complications.

Inhaled Epinephrine and Oral Theophylline–Ephedrine in the Treatment of Asthma

Jacob L. Pinnas, MD, Bernard P. Schachtel, MD, Tien Min Chen, MS, H. Randall Roseberry, and William R. Thoden, MA

Inhaled and oral over-the-counter bronchodilators are used for self-therapy by asthmatic patients. To evaluate their safety and efficacy, we compared epinephrine and theophylline combined with ephedrine with inhaled metaproterenol and the placebo. Twelve asthmatic patients were studied in a randomized, double-blind, placebo-controlled, crossover trial comparing forced expiratory volume in 1 second (FEV_1) after two inhalations of epinephrine (0.2 mg/inh), 1 minute apart, followed in 15 minutes by theophylline (130 mg) with ephedrine (24 mg) versus two inhalations of metaproterenol (0.65 mg/inh), 1 minute apart, versus placebo inhaler and tablets. Onset of FEV_1 > 15% above baseline values occurred within 15 seconds after inhalations for 100% of epinephrine-treated patients, 92% of metaproterenol-treated patients, and 33% of placebo-treated patients. FEV_1 responses were significantly greater ($P < .05$) for epinephrine at 0.66 to 1.66 minutes compared with the responses of metaproterenol, and epinephrine and theophylline that was combined with ephedrine compared with metaproterenol beginning at 2 hours. Mean duration of activity was 5.7 hours for the epinephrine- and theophylline with ephedrine-treated patients, 4.9 hours for metaproterenol-treated patients, and 2 hours for the placebo group. There were statistically significant differences for patients receiving epinephrine and theophylline with ephedrine versus the placebo group ($P < .001$), metaproterenol patients versus the placebo group ($P = .02$), and patients receiving epinephrine and theophylline with ephedrine versus metaproterenol-treated patients ($P < .05$). Compared with inhaled metaproterenol, inhaled epinephrine followed in 15 minutes by a theophylline–ephedrine tablet had a significantly earlier onset, longer duration of action, numerically greater peak effect, and patient preference. This combination of oral and inhaled bronchodilator medication is as safe and effective as inhaled metaproterenol.

Inhaled and oral bronchodilator drug products such as inhaled epinephrine and a theophylline–ephedrine tablet have been available over the counter for many years and used extensively by asthmatic patients as separate modes of self-therapy.[1] However, efficacy of the combined therapy by these two bronchodilator drug products has not been evaluated. Therefore, we conducted a placebo-controlled crossover trial to evaluate the efficacy of the combination therapy regimen. In the trial, inhaled epinephrine was followed by oral theophylline with ephedrine and compared with another bronchodilator, inhaled metaproterenol sulfate, which reportedly improved respiratory function for at least 4 hours[2–5] in a group of asthmatic patients with reversible bronchospasm.

From the Department of Internal Medicine, Tucson, Arizona (Dr. Pinnas, Ms. Chen, Mr. Roseberry) and the Medical Department, Whitehall Laboratories, Inc., New York, New York (Mr. Thoden, Dr. Schachtel). Presented in part at the 53rd Annual Scientific Assembly of the American College of Chest Physicians, October 27, 1987, Atlanta, GA. Address for reprints: Jacob L. Pinnas, MD, 1501 North Campbell, Tucson, AZ 85724.

MATERIALS AND METHODS

Patient Selection

All patients were required to have a diagnosis of moderate-to-severe asthma with reversible bron-

chospasm measured as a forced expiratory volume in 1 second (FEV_1) that was between 30% and 80% of the predicted normal FEV_1.[6,7] Reversibility was defined as an increase of at least 15% in FEV_1 after inhaling 0.5 mL of a 1:200 isoproterenol aerosol solution. Patients were excluded who had a history of hypersensitivity to epinephrine, theophylline, ephedrine, or metaproterenol; symptomatic cardiovascular disease, impaired renal function, liver disease, diabetes mellitus, hypothyroidism, or chronic obstructive pulmonary disease; or who were taking antidepressant medication or corticosteroids. The following washout periods for antiasthmatic medications were maintained before each of the treatment visits: sodium cromolyn within 2 weeks, long-acting oral bronchodilators within 48 hours, and aerosol bronchodilators within 12 hours.

The Human Subjects Committee of the University of Arizona approved the study design, and all patients provided written informed consent.

Study Design

Twelve patients entered and completed all three treatment periods of this double-blind, placebo-controlled, crossover study. Patients who met the admission criteria were assigned by a computer-generated randomization code to receive in random order each of three treatment regimens: (1) two inhalations 1 minute apart of epinephrine (0.2 mg/inh) followed at 15 minutes by a tablet containing theophylline (130 mg) and ephedrine (24 mg); (2) two inhalations 1 minute apart of metaproterenol sulfate (0.65 mg/inh) followed at 15 minutes by a placebo tablet; (3) two inhalations 1 minute apart of a placebo mist (vehicle without active medication) followed at 15 minutes by a placebo tablet (identical in appearance to the theophylline–ephedrine tablet).

At screening, each patients' medical history of asthma was confirmed, and a physical examination was performed, including radial pulse, blood pressure, respiratory rate, and lung sounds. Pulmonary function tests included spirometric measurement (best of three readings) of FEV_1, forced vital capacity (FVC), and peak expiratory flow rate (PEFR). These tests were repeated after a single 0.5-mL inhalation of a 1:200 isoproterenol aerosol solution to determine reversibility (≥15% increase in FEV_1).

At each of the three treatment visits, the same procedure was followed. Radial pulse, FEV_1, FVC, and PEFR were measured before the patient took the study medication. At each visit, the patient's FEV_1 was required to be within 30% to 80% of the predicted normal value and within 20% of all preceding baseline FEV_1 measurements for the patient. At the time of qualification, each patient was given the first inhalation of the randomly assigned study medication, and post-treatment response of FEV_1 was evaluated at 0.25, 0.66, and 1 minute after inhalation. A second inhalation was given immediately after the 1-minute spirometry, and FEV_1 was evaluated again 1.25, 1.66, 2, 5, and 15 minutes after the first inhalation. Immediately after the 15-minute spirometry, each patient swallowed the assigned tablet, and FEV_1 was evaluated at 45, 75, 135, 195, 255, 315, and 375 minutes after the first inhalation. Pulse rate was recorded at each post-treatment interval. At the conclusion of each treatment period, the patient was asked to evaluate the medication on an ordinal scale (1–10) in response to the question, "Considering the effect today's treatment has had on your breathing over the past 6 hours, how would you rate it as a treatment for asthma?" Patients returned at weekly intervals for the other two treatment periods. Adverse effects were recorded at any time during each treatment period.

Statistical Analysis

The time to onset of response for each treatment (defined as the first observable time when improvement in FEV_1 was >15% above baseline), the duration of time that FEV_1 was >15% above baseline, and the peak percent change in FEV_1 were analyzed using analysis of variance and the two-tailed Mann–Whitney U-test. Analysis of variance and Duncan's multiple range test were used to compare percent change from baseline for FEV_1 and mean area under the FEV_1 time–effect curve. Global evaluation scores were analyzed by analysis of variance and Wilcoxon signed rank tests. A P value $< .05$ was considered statistically significant. All values given are mean ± standard deviation.

RESULTS

Mean pulmonary function values and pertinent clinical features at the time of entry in the study for the 12 patients (six men, six women) are shown in Table I. The patients ranged in age from 19 to 57 years, had an average of 55% of predicted FEV_1, and showed an average 51% improvement in FEV_1 after receiving isoproterenol. The mean pretreatment FEV_1 values for the three treatments were similar: epinephrine with theophylline–ephedrine (2.0 ± 0.6 *L*), metaproterenol with placebo (2.1 ± 0.7 *L*), and placebo (2.0 ± 0.7 *L*).

The percent change in FEV_1 for each treatment at each post-treatment interval is shown in Table II. The mean time to onset of action was 0.66 ± 0.31

TABLE I

Clinical Features of 12 Patients at Time of Entry in Study

Variable	Mean ± SD	(Range)
Age	33 ± 12 yrs	(19–57 yrs)
Height	175 ± 10 cm	(163–193 cm)
Weight	78 ± 15 kg	(55–103 kg)
Radial pulse	78 ± 6 bpm	(72–88 bpm)
Systolic blood pressure	112 ± 8 mm Hg	(100–128 mm Hg)
Diastolic blood pressure	67 ± 7 mm Hg	(60–82 mm Hg)
FEV_1	2.1 ± 0.8 L	(1.0–3.9 L)
% Predicted FEV_1	55 ± 14	(30–80%)
FVC	3.6 ± 1.1 L	(2.4–5.1 L)
PEFR	3.3 ± 1.0 L/min	(1.3–5.7 L/min)
% Improvement in FEV_1 on isoproterenol	51 ± 33	(16–144%)

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEFR = peak expiratory flow rate.

TABLE II

Percent Change in FEV_1 at Each Post-Treatment Evaluation (mean ± SD)

Evaluation Time (min)	Treatment—Percent Change: Epinephrine + Theophylline–Ephedrine‡	Metaproterenol§	Placebo¶
0.25	11 ± 17	6 ± 14	2 ± 23
0.66	26 ± 19*†	11 ± 13	4 ± 18
1.0	33 ± 21*†	18 ± 8*	−3 ± 16
1.25	38 ± 20*†	23 ± 10*	4 ± 19
1.66	40 ± 15*†	24 ± 11*	1 ± 19
2.0	44 ± 25*	31 ± 10*	2 ± 21
5.0	47 ± 29*	40 ± 11*	1 ± 23
15.0	41 ± 25*	38 ± 13*	3 ± 26
45.0	42 ± 28*	39 ± 17*	11 ± 28
75.0	46 ± 31*	37 ± 19*	11 ± 29
135.0	53 ± 26*†	33 ± 18	18 ± 23
195.0	56 ± 34*†	25 ± 22	12 ± 28
255.0	53 ± 28*†	20 ± 16	11 ± 30
315.0	45 ± 27*†	15 ± 18	12 ± 20
375.0	43 ± 32*†	12 ± 20	14 ± 20

** P < .05 vs. placebo*
† P < .05 vs metaproterenol
‡ 0.2 mg/inhalation at time 0 and 1 minute followed at 15 minutes by a theophylline 130 mg with ephedrine 24 mg tablet
§ 0.65 mg/inhalation at time 0 and 1 minute followed at 15 minutes by a placebo tablet.
¶ Placebo inhalation at time 0 and 1 minute followed at 15 minutes by a placebo tablet.

minutes for epinephrine ($P < .01$ vs. placebo), 0.96 ± 0.41 minutes for metaproterenol ($P = .02$ vs. placebo), and 230.3 ± 182.7 minutes for placebo; epinephrine was active at 0.66 minutes (numerically but not statistically significantly) faster than metaproterenol ($P = .08$), as shown in Figure 1. Within 15 seconds after two inhalations, 100% of epinephrine-treated patients and 92% of metaproterenol-treated patients had a >15% improvement over baseline, significantly more than the placebo group (33%; $P < .05$), and a difference that indicated a faster onset of action of epinephrine compared with metaproterenol ($P < .05$).

The mean duration of action (Figure 2) for epinephrine followed by theophylline with ephedrine was 5.7 ± 1.7 hours, significantly greater than for the placebo group (2.0 ± 2.8 hrs; $P < .001$). The mean duration of action of those patients receiving metaproterenol (4.9 ± 1.9 hrs) was also significantly different from that of the placebo group ($P = .02$). The duration of action for the patients receiving the combination regimen was significantly longer than for those taking metaproterenol ($P < .05$). From 135 minutes to the end of the study, the percent increase in FEV_1 for patients treated with epinephrine and theophylline with ephedrine was significantly greater than for those patients receiving metaproterenol ($P < .05$; Table II). The maximum percent improvement in FEV_1 for those receiving epinephrine plus theophylline with ephedrine (62 ± 32%)

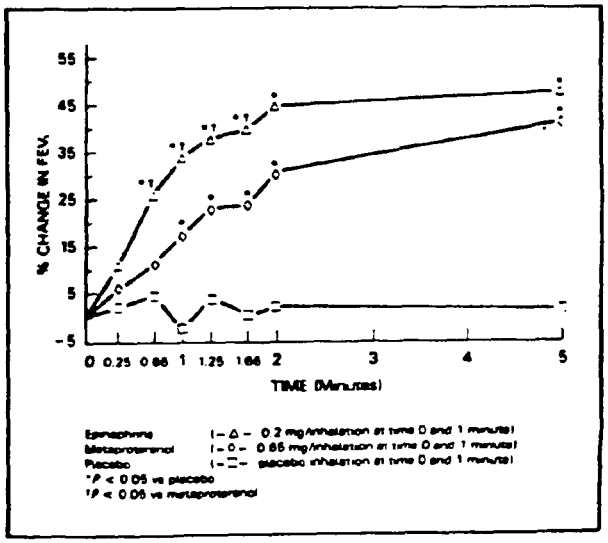

Figure 1. Percent change in FEV_1 from baseline over the first 5 minutes post-treatment.

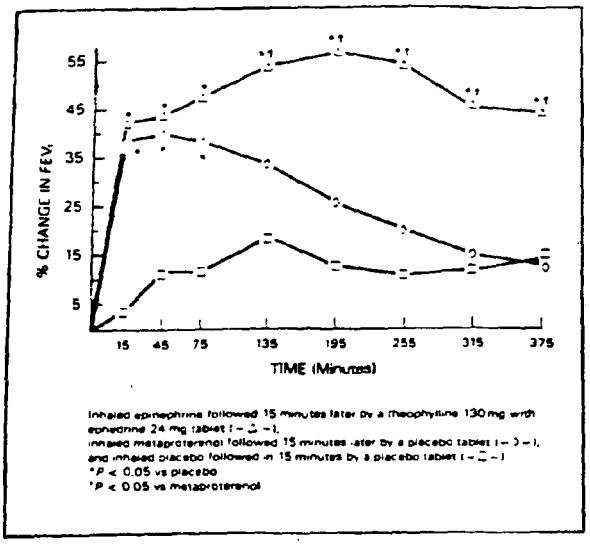

Figure 2. Percent change in FEV, from baseline at 15 to 375 minutes post-treatment.

was significantly greater than for the placebo group (25 ± 26%; $P < .01$) as well as for patients receiving metaproterenol (45 ± 14%) compared with the placebo group ($P < .05$). The mean area under the time-effect curve (Figure 2) for $FEV_1 > 15\%$ above baseline for those patients receiving epinephrine plus theophylline with ephedrine was 231 ± 152 L-min, significantly greater than for the placebo group (70 ± 116 L-min; $P < .01$). The mean for metaproterenol patients (128 ± 110 L-min) was also significantly different from that for the placebo group ($P < .05$). By this determination of overall bronchodilator effect, the combination regimen provided a (numerically but not statistically significantly) longer duration of action than metaproterenol ($P = .08$).

On the global evaluation of efficacy (Figure 3), patients rated epinephrine followed by theophylline with ephedrine higher (7.5 ± 2.3) than the placebo (2.5 ± 1.5; $P < .001$). They also rated metaproterenol (5.8 ± 2.4) higher than the placebo ($P < .005$). These symptomatic ratings also numerically (but not statistically) distinguished epinephrine plus theophylline with ephedrine from metaproterenol ($P = .07$).

There were no clinically significant effects on heart rate during the epinephrine treatment phase, the theophylline with ephedrine phase, or the metaproterenol phase. Adverse reactions were reported by four patients: one patient experienced tremors while receiving epinephrine plus theophylline with ephedrine and also while receiving metaproterenol; one experienced itching while receiving metaproterenol and also while receiving placebo; one experienced nervousness while receiving placebo; and one experienced headache and vomiting while receiving placebo. None of these adverse effects required treatment.

DISCUSSION

The results of this double-blind, randomized, crossover study can be viewed in two ways. First, during the initial 15 minutes of the observation period, two inhalations of epinephrine were compared with two inhalations of an active aerosol, metaproterenol, as a positive control, and with placebo, as a negative control. Greater increases in FEV_1 were registered by patients receiving epinephrine than those receiving metaproterenol or placebo, and significantly more patients showed a faster onset of bronchodilator action while receiving epinephrine than metaproterenol ($P < .05$). The benefits of these two types of aerosol therapy in the treatment of asthma are clear.[6-11] Because they represent the direct topical application of the drug, aerosols provide specific local bronchial action and prompt onset of therapeutic response. Additionally, because aerosols require a relatively small dose of drug to provide a therapeutic effect, unwanted systemic absorption of the drug and adverse effects are minimized. Indeed, all three treatment groups had a similar incidence of adverse effects, and neither inhaled epinephrine nor inhaled

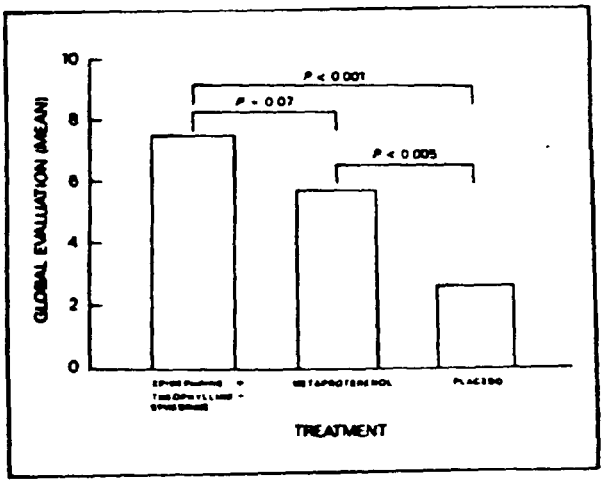

Figure 3. Patients' global evaluation of each study medication rated on a scale of 1 = poor to 10 = excellent.

metaproterenol had a consistent or clinically significant effect on heart rate. The results of this phase of the study clearly show a rapid onset of action of inhaled epinephrine without adverse effects.

Second, the entire 6-hour trial permits an evaluation of the efficacy of epinephrine followed at 15 minutes by a tablet containing theophylline with ephedrine. When compared with placebo treatment, the combination regimen produced significant bronchodilation, which lasted throughout the 6-hour trial. This duration of action was significantly longer than that for metaproterenol, confirming the efficacy of this combined over-the-counter bronchodilator regimen. Indeed, 6 hours after tablet administration, the increase in FEV_1 on the over-the-counter combination therapy was still significantly different from metaproterenol and placebo ($P < .05$), whereas metaproterenol was no longer active compared with placebo. Overall, the bronchodilatory effect of the combination was confirmed by the patients, who rated it more effective for their breathing: significantly better than placebo and numerically better than metaproterenol.

The results of this study also indicate that theophylline (130 mg) with ephedrine (24 mg) is an effective bronchodilator agent. Although the bronchodilating effect of the tablet would have been more clearly tested by comparison with an inhaled epinephrine–placebo tablet treatment group, the short duration of action in patients who inhaled epinephrine, 2 to 3 hours,[4] strongly suggests that the maintained bronchodilating effect in the epinephrine/theophylline–ephedrine treatment group after 2 to 3 hours is attributable to the combination tablet. This study confirms the findings of other investigators.[12-14] The lack of side effects for the patients who received the combination treatment attests to its safety.

In summary, these findings demonstrate the safety and efficacy of over-the-counter bronchodilator therapy, inhaled epinephrine, and oral theophylline with ephedrine, when compared with inhaled metaproterenol and placebo under the conditions of the study. Furthermore, this over-the-counter combination regimen had a rapid onset, long duration of action, high peak effect, and excellent patient perception of effectiveness.

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Systemic absorption of inhaled epinephrine

To determine the systemic absorption of epinephrine when it is given by inhalation, six normal volunteers were given 15 puffs, followed by 30 puffs, of epinephrine from a pressurized aerosol (160 μg epinephrine/puff). The peak mean (±SE) plasma epinephrine levels were 1.50 (±0.61) and 4.22 (±1.93) nmol/L 1 minute after each dose, respectively. The effect on physiologic finger tremor correlated with the plasma epinephrine level and returned to baseline 20 minutes after taking the higher dose. There was a small fall in mean plasma potassium levels of 0.45 mmol/L and a small rise in plasma glucose levels of 0.81 mmol/L. On a separate occasion an injection of 0.3 ml of 1/1000 (300 μg) epinephrine was given subcutaneously to the same individuals. This caused a peak plasma epinephrine level of 2.43 (±0.47) nmol/L at 10 minutes, and this was still raised at 2.05 (±0.41) nmol/L after 40 minutes. The maximum fall in the mean plasma potassium level was 0.43 mmol/L after the injection. (CLIN PHARMACOL THER 1986;40:673-8.)

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The increase in deaths as a result of asthma in the United Kingdom during the 1960s, when considerable concern was expressed about isoprenaline aerosol,[1] highlighted the need to assess the systemic absorption of inhaled drugs. This point has recently been reemphasized when the increase in deaths caused by asthma in New Zealand led to the probably erroneous suggestion that nebulized β-agonists are dangerous.[2] Despite these concerns, remarkably little data exist on the systemic blood levels of inhaled drugs, mainly because of difficulties in drug assay technique.

When an aerosol is inhaled, the majority of the drug is subsequently either exhaled or deposited in the mouth and swallowed. Only 10% to 15% reaches the lungs[3,4] where significant systemic absorption may occur. When epinephrine is used, fewer side effects are seen with the inhaled route,[5] and urinary excretion suggests that only one tenth of the inhaled drug is absorbed when compared with the same dose given by subcutaneous injection.[5]

For the treatment of anaphylaxis, subcutaneous epinephrine remains the drug of choice.[5,6] However, patients may have acute urticarial attacks at some distance from medical help. In these cases, self-injection of epinephrine is often prescribed. This is thought to be the best route of dosing, although inhaled epinephrine has been advocated.[7] Apart from being easier for the patient, the inhaled route also has the advantage of direct contact with the larynx (where life-threatening edema may occur) together with rapid relief of associated bronchospasm. However, it is possible that severe airway obstruction may interfere with drug inhalation and hence absorption.

Inhaled epinephrine was chosen for the present study partly as an example of inhaled β-agonist drugs in general and partly to determine its theoretic potential in the treatment of anaphylaxis. Systemic absorption was assessed by measuring plasma epinephrine, potassium, and glucose levels, heart rate, and physiologic finger tremor. Finger tremor was chosen because it is readily influenced by β_2-adrenoceptor stimulation[8-10] and low doses of epinephrine stimulate predominantly β_2- rather than β_1-receptors.[11] The effects of epinephrine inhalation were compared with a subcutaneous injection of 300 μg of epinephrine, a dose that is within the range recommended for the treatment of anaphylaxis[6] and is also commonly used in the treatment of acute asthma.[12,13]

METHODS

Six normal healthy male hospital personnel, who gave informed consent, were studied. The protocol was

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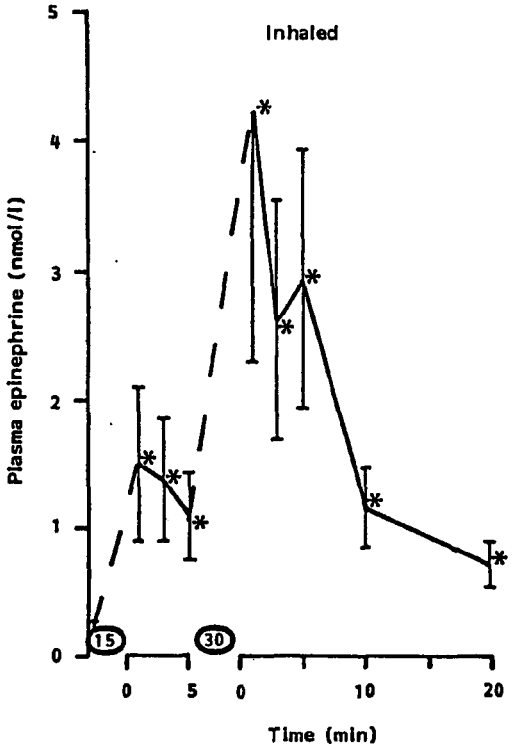

Fig. 1. Effect of epinephrine inhalation on plasma epinephrine levels. Values are the mean ± SE of six subjects. (*P < 0.05 cf baseline; 15 = 15 inhalations of epinephrine aerosol [160 μg/puff]; 30 = 30 inhalations of epinephrine aerosol [160 μg/puff].)

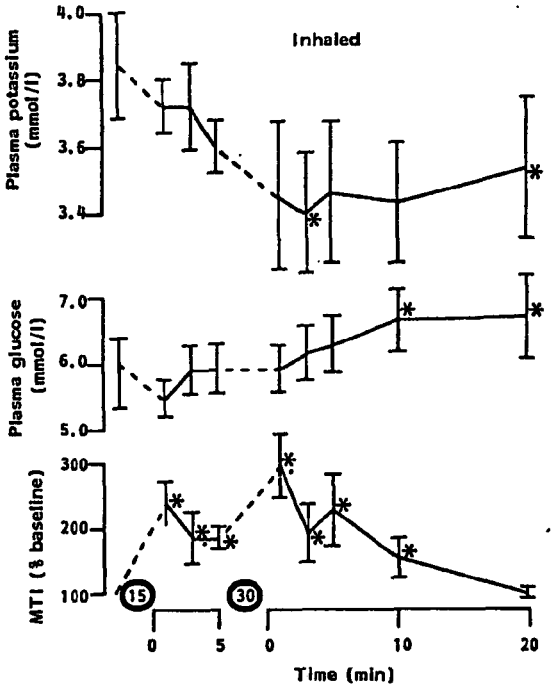

Fig. 2. Effect of epinephrine inhalation on MTI and plasma glucose and potassium levels. (Same experiment as Fig. 1.)

approved by the Hospital Ethics Committee. The average age was 26 years (range 24 to 32), mean weight 71 kg (range 65 to 81), and height 1.74 m (range 1.70 to 1.77). All were nonsmokers and receiving no medical treatment. They were each studied on 2 days 1 week apart at the same time of day. On one occasion they received inhaled and on the other subcutaneous epinephrine; the order was randomized. They abstained from tea or coffee for 4 hours before each experiment.

On arrival in the laboratory an intravenous cannula was inserted into a left forearm vein for blood sampling. Physiologic finger tremor was measured by an accelerometer (Specialized Laboratory Equipment Ltd., Croydon, U.K.). This was taped to the dorsum of the distal interphalangeal joint of the right index finger. It was connected to a Mingograf '10' EEG ink-jet paper recorder (Elema-Schönander AB, Sweden). The right forearm was held in the prone position and supported up to the metacarpophalangeal joints on the arm rest of the chair. The fingers were held straight and the metacarphophalangeal joints were flexed at 30 degrees from the horizontal position. Because of the considerable individual variation in tremor amplitude, the sensitivity of the Mingograf recorder was adjusted to give a satisfactory baseline record. The baseline reading was repeated three times before each experiment and the mean of these was taken as 100%. No baseline reading exceeded the mean of the three baseline readings by more than 20%.

Tremor amplitude was measured as a percentage change from the individual's baseline and expressed as mean tremor index (MTI). To calculate tremor activity, a line was drawn through the center of a typical piece of trace. The amplitude of five consecutive waves above this line and the five corresponding waves below the line was measured, and the mean of these 10 measurements constituted one reading. Analysis of the tremor trace was carried out without knowledge of the plasma epinephrine levels.

The subject sat in a wheelchair throughout so that he could be wheeled into the corridor to inhale epinephrine. This prevented contamination of the collecting equipment by epinephrine aerosol, an important con-

sideration because of the sensitivity of the assay. After a 20-minute rest period, baseline tremor was recorded and a blood sample drawn. Heart rate was determined by counting the radial pulse for 30 seconds. The subject then either received 0.3 ml 1/1000 epinephrine (300 μg) subcutaneously over the deltoid or was wheeled into the corridor to take inhalations of epinephrine acid tartrate (Medihaler-epi, Riker, U.K.; 160 μg epinephrine base/inhalation). Before the experiment, full instruction was given in inhaler technique. The subjects inhaled the aerosol by breathing in from near-residual lung volume to total lung capacity and holding their breath for 2 seconds. They took five puffs in consecutive breaths and then waited 30 seconds before the next five doses to prevent symptoms of hyperventilation. After 15 supervised inhalations they were wheeled back into the laboratory. One, 3, and 5 minutes later, heart rate and tremor were recorded and blood was drawn. They were then wheeled back into the corridor to take an additional 30 inhalations, starting within 1 minute of the previous 5-minute readings, and measurements were repeated 1, 3, 5, 10, and 20 minutes later. When subcutaneous epinephrine was given, the same baseline measurements were taken and then repeated 5, 10, 15, 22.5, and 30 minutes after injection.

For epinephrine estimation, 5 ml of blood was placed in a chilled lithium-heparin tube containing 100 μl of a mixture of reduced glutathione and EGTA. The sample was stored on ice and separated by cold centrifuge within 20 minutes of being taken. Plasma was stored at −70° C until assayed by a radioenzymatic method,[14] with an intra-assay coefficient of variation of 4% and an interassay coefficient of variation of 6%. This was calculated on a standard plasma sample with a mean adrenaline concentration of 0.41 nmol/L. The carryover of noradrenaline into the adrenaline assay was 0.3%. Plasma glucose and potassium levels were estimated on the same sample by a routine glucose oxidase and a flame photometer method, respectively.

RESULTS

Fig. 1 shows the effect of inhaled epinephrine on plasma epinephrine, and Fig. 2 shows its effect on plasma potassium, plasma glucose, heart rate, and MTI. After 15 inhalations of epinephrine the mean (SE) baseline epinephrine level rose from 0.23 (0.02) to a peak plasma level of 1.50 (0.61) nmol/L at 1 minute, and 1 minute after 30 inhalations this had risen to 4.22 (1.93) nmol/L. The corresponding peak MTI values were 237% (34%) and 294% (50%). The maximum fall from baseline of the mean plasma potassium level occurred 3 minutes after 30 inhalations and was 0.45 mmol/L.

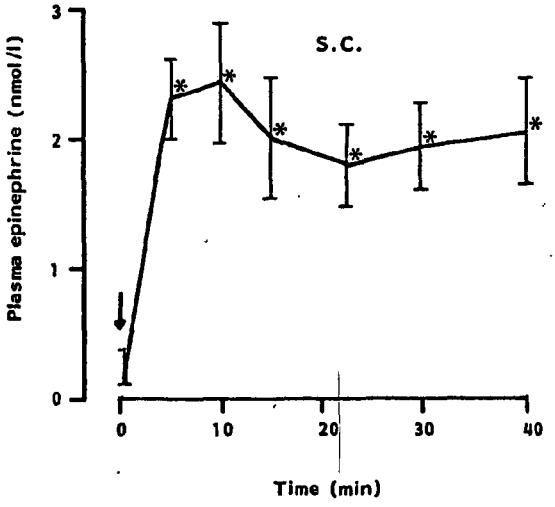

Fig. 3. Effect of subcutaneous *(SC)* epinephrine injection on plasma epinephrine levels. Values are mean ± SE of six subjects. (*P < 0.05 cf baseline; ↓ = time of injection.)

The maximum increase in mean plasma glucose values was 0.81 mmol/L above baseline 20 minutes after 30 inhalations. Plasma epinephrine and MTI fell to baseline 20 minutes after 30 inhalations of epinephrine, although plasma glucose levels appeared to be still rising. All values are mean (SE). Statistical significance was calculated according to the Wilcoxon signed-rank test.

Figs. 3 and 4 show the effect of subcutaneous injection of epinephrine on the same parameters as in Figs. 1 and 2. The peak epinephrine level occurred 10 minutes after injection and was 2.43 (0.47) nmol/L with a corresponding peak MTI level of 255% (63%). These had fallen to 2.05 (0.41) nmol/L and 208% (91%), respectively, by 40 minutes. The maximum fall in the mean plasma potassium level from baseline was 0.43 mmol/L 40 minutes after injection, although the potassium level may have fallen and the plasma glucose level risen further if the experiment had been continued.

The maximum increase in mean heart rate above baseline was 7 bpm after subcutaneous epinephrine and 9 bpm after inhaled epinephrine. Although heart rate gave little indication of systemic absorption, the MTI showed a good correlation with plasma epinephrine. No subject reported significant side effects other than pain at the site of injection.

It is possible that the subcutaneous injection caused an increase in endogenous epinephrine release. To check this we performed a pilot study on three normal

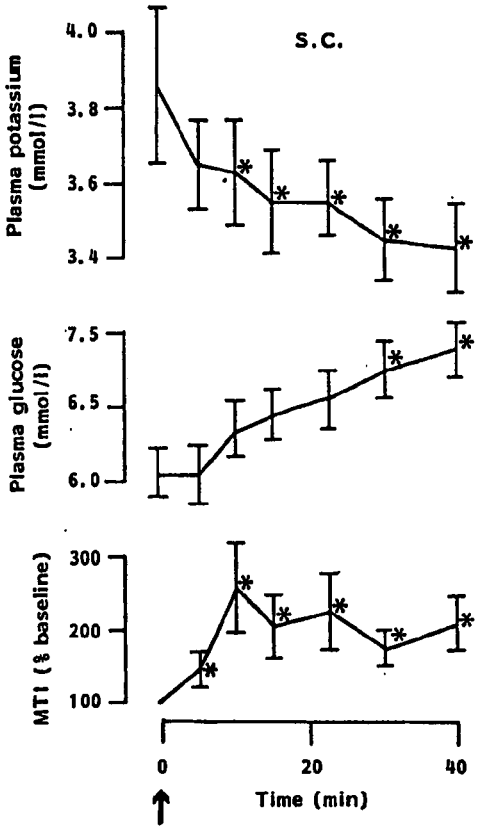

Fig. 4. Effect of subcutaneous *(SC)* epinephrine injection on MTI and plasma glucose and potassium levels. (Same experiment as Fig. 3.)

healthy men who received double blind either 0.3 ml of 1/1000 epinephrine or 0.3 ml of saline solution as placebo. We found that there was no elevation in plasma epinephrine values with placebo, and this is in keeping with other studies that showed that moderate levels of stress do not increase epinephrine secretion.[15] We also checked the effect of placebo inhalation on MTI and found that up to 45 inhalations produced no significant effect.

The design of the experiment makes AUC measurements inaccurate because the epinephrine level did not return to baseline after either subcutaneous injection or 15 inhalations. We nonetheless felt it was important to estimate approximately the proportion of inhaled epinephrine that was absorbed when compared with the amount of epinephrine absorbed in the first 20 minutes after injection. The AUC was calculated for the inhaled experiment as the area above the baseline epinephrine level for the 20 minutes after 30 puffs of epinephrine. The corresponding area was also measured for the first 20 minutes after the injection. The two curve areas were compared with the difference in epinephrine dose being taken into account. This comparison suggested that if a unit dose of epinephrine was given, the inhaled route would be only 5% as effective in terms of systemic absorption in the first 20 minutes when compared with the subcutaneous route.

DISCUSSION

Despite considerable worldwide interest in the side effects of inhaled β-agonists,[1,2,16,17] data on the plasma levels of these drugs are scarce. The small quantities of drug involved make their assay technically difficult. The systemic absorption of inhaled epinephrine has been studied before, but an early fluorometric assay was used that gave satisfactory results only on urine samples.[5] The development of accurate radioenzymatic assays for plasma epinephrine[18] makes this drug a good model to use. Epinephrine has α-agonist activity, and it is possible that vasoconstriction may affect its absorption from the lung. Therefore our findings do not necessarily relate to other, more specific β-agonist drugs.

The present study shows that appreciable quantities of epinephrine may be absorbed by the inhaled route if adequate doses are given. However, even with 30 doses of the metered-dose aerosol, serious toxicity was not observed and the systemic effects wore off after 20 minutes. An important proviso is that systemic absorption showed considerable individual variation and this may be more marked in patients with anaphylaxis or acute airways obstruction. Although many authors have suggested that aerosol overusage may contribute to increased death in asthma, this appears not to be the case. After an initial correlation between aerosol prescribing and asthma deaths in the United Kingdom in the 1960s, the number of aerosol β-agonist drugs sold has continued to rise, although the incidence of asthma deaths has fallen.[19] The concern about inhaled β-agonists probably stems from the use of "isoforte" (isoproterenol, 400 μg/inhalation) because in normal subjects just three inhalations of this preparation produce an average increase in heart rate of 44 bpm.[20] In the present experiment 30 inhalations of epinephrine produced an increase in mean heart rate of only 9 bpm. In this respect, epinephrine aerosol is similar to the more selective β_2-agonist drugs such as terbutaline aerosol, 63 puffs of which caused a mean increase in heart rate of only 16 bpm.[21]

Systemic β-agonists have been known to induce hy-

pokalemia for some time,[22] and even low doses of epinephrine can induce a significant fall in plasma potassium levels.[23] Inhaled β-agonist bronchodilators may also reduce hypokalemia,[16] and our study shows that inhaled epinephrine may cause a small fall in potassium levels if we gave many times the recommended dose. The fall in potassium levels was similar to that induced by a standard dose of subcutaneous epinephrine but smaller than that caused by a small dose of fenoterol.[15] The maximum fall in mean plasma potassium level was 0.45 mmol/L and on its own is unlikely to be clinically significant.

We measured just the heart rate as an index of cardiac effects because the pilot experiment suggested that injected epinephrine caused only low plasma levels. Other studies have also shown that similar doses of subcutaneous epinephrine have very little cardiovascular effect.[24] We have previously shown that low levels of epinephrine have predominantly β_2 effects,[11] and therefore we chose to measure physiologic finger tremor and blood glucose and potassium levels as parameters of β_2 stimulation.

Subcutaneous epinephrine is still widely used in the emergency room for the treatment of acute asthma in the United States, yet we are not aware of any other data on the plasma levels that result. Our data were not collected for long enough to give a full-time course of the pharmacokinetics of this treatment, but the experiment does demonstrate that the plasma level is significantly elevated at 20 minutes. Furthermore, effects on plasma glucose and potassium levels lag behind the plasma epinephrine level. Therefore the usual practice of repeating the injection of 300 μg every 20 minutes[12] is likely to have a cumulative effect, and this could well cause serious hypokalemia in some individuals. We did not standardize the diet of the subjects nor study them fasting, and interpretation of the potassium and glucose data should take this into account. It has been suggested that only one injection of a low dose of epinephrine should be used in acute asthma and this should not be repeated at 20-minute intervals[25] because its bronchodilator effect is often prolonged. Our data support this view because repeated injection at 20-minute intervals may lead to accumulation and hence toxicity. The small area from which the injection is absorbed contrasts with the large area of the airway from which the inhaled drug may enter the circulation. This undoubtedly accounts for the much more rapid peak and shorter duration of the inhaled epinephrine; the subcutaneous route will also be delayed by local vasoconstriction.

When epinephrine is instilled into the trachea of an anesthetized dog it is rapidly absorbed,[26] and it has been suggested that absorption by the lung is sufficient to recommend the inhaled route as a suitable mode of treatment for acute urticarial reactions.[7,27] In favor of the inhaled route is that the greatest danger from anaphylaxis arises from the accompanying bronchospasm and laryngeal edema. The direct contact of the spray to these areas may outweigh the disadvantage of high variability in systemic absorption. Obviously this depends on the patient being sufficiently well enough to coordinate the inhaler.

This is the first study we are aware of that compares the inhaled and systemic routes of dosing on the plasma levels of a β-agonist drug. The inhaled route gives rapid and adequate systemic absorption of epinephrine if a high enough dose is used. However, inhaled epinephrine in conventional doses may be expected to have far less toxicity than subcutaneous epinephrine in treating acute asthma. Inhalation may prove to be a preferable mode of dosing for the self-treatment of anaphylaxis and acute urticaria, although systemic absorption shows greater variation than when adrenaline is given by subcutaneous injection.

We thank Dr. L. Youlten, Professor P. Sever, and the Neurology Department at St. Mary's Hospital.

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APPENDIX 2

Asthma Treatment Guideline from the National Heart, Lung and Blood Institute, 2002

Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment

Classify Severity: Clinical Features Before Treatment or Adequate Control	Symptoms/Day Symptoms/Night	PEF or FEV_1 PEF Variability	Medications Required To Maintain Long-Term Control Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled $beta_2$-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% – < 80% > 30%	■ Preferred treatment: – Low-to-medium dose inhaled corticosteroids and long-acting inhaled $beta_2$-agonists. ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled $beta_2$-agonists. ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	≥ 80% 20–30%	■ Preferred treatment: – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80% < 20%	■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Quick Relief
All Patients

- Short-acting bronchodilator: 2–4 puffs short-acting inhaled $beta_2$-agonists as needed for symptoms.
- Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed.
- Use of short-acting $beta_2$-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

Step down
Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

Step up
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled $beta_2$-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV_1 is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled $beta_2$-agonists. Overreliance on short-acting inhaled $beta_2$-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

APPENDIX 3 – SAFETY REPORT

SAFETY QUERY RESPONSE FOR REQUEST FROM WYETH CONSUMER HEALTHCARE REGARDING FATAL EVENTS COINCIDENT WITH THE USE OF PRIMATENE MIST (EPINEPHRINE) AND PRIMATENE TABLETS (EPHEDRINE WITH GUAIFENESIN AND THEOPHYLLINE WITH GUAIFENESIN)

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Introduction

As a result of a request from Wyeth Consumer Healthcare regarding fatal events coincident with the use of Primatene Mist (epinephrine) and Primatene Tablets (ephedrine with guaifenesin and theophylline with guaifenesin), Wyeth Global Safety Surveillance & Epidemiology (GSSE) conducted a search of the Safety Surveillance System (S^3) database.

Safety Surveillance System Database (S^3) & Wyeth consumer healthcare database

The S^3 database contains adverse experience reports for Wyeth's marketed products, foreign and domestic, received from health care professionals (HCP), consumers, registries, licensing partners, and the medical literature. Additionally, the S^3 database contains serious adverse experience reports from investigational studies involving Wyeth products.

An all-time search of S^3 through 28 July 2005[1] was conducted for spontaneous, study, medically and non-medically confirmed cases of fatal outcomes with the reporting, suspect or concomitant products ephedrine/guaifenesin and epinephrine.

In addition, the Wyeth Consumer Healthcare (WCH) Drug Safety Evaluation Department searched the WCH database for fatal cases for the products ephedrine/guaifenesin, theophylline/guaifenesin and epinephrine.

General Description of Cases

A total of 28 reports involving 33 fatal outcomes coincident with the use of Primatene Mist were found. In 1 consumer case, the reporter states that a pharmacist stated that the product "had caused 6 deaths." One of the cases involved the use of both Primatene Mist and Primatene Tablets as concomitant medications. Further details of the cases are provided in the Summary Table of Fatal Reports.

[1] S3 became operational 4th Q 1999. Adverse event information, excluding source documents, for NDA products from 1995 to the initiation of the S3 database was transferred/entered into S3. Information prior to 1995 is contained in the Wyeth Consumer Healthcare database (previously Whitehall Robins).

Of the 28 cases, 19 were consumer reports, 8 were HCP reports and one case was from the medical literature. Of the eight HCP reports, six were from Medical Examiners or Coroners.

Ages were provided in 10 cases and ranged from 17 to 66 years of age (median = 32.5). Twenty-four cases provided gender information; there were 9 male and 15 female cases.

Of the 19 consumer reports, 12 (including 1 suicide, 1 overdose, 1 intentional misuse, and 1 drug administration error) provided an insufficient amount of information for assessment. Of the remaining 7 cases, there was 1 drug dependence, 1 suicide and 1 case of a hemorrhagic stroke due to hypertensive and atherosclerotic cardiovascular disease. The remaining 4 cases are summarized in Section 2.2 below.

Of the 8 HCP reports, 1 provided an insufficient amount of information for assessment, 1 was an overdose, and 1 was an alcohol-related motor vehicle. The remaining 5 cases are summarized below.

The medical literature report was described as an intentional misuse and intentional overdose.

Summaries of Remaining Cases

Four consumer cases and 5 HCP cases that provided some detailed information and were not cases of drug dependence, suicide, overdose, misuse, drug administration error, or confounding by nature of death are summarized below.

- A medical examiner case (8-95235-009C) of a 32-year-old woman with a history of chronic asthma reports that the patient used Primatene Mist at 10-11pm due to dyspnoea and awoke the following morning at 4am with difficulty breathing. The patient collapsed and was taken to the hospital. She was 7 months pregnant and 2 healthy twin girls were delivered via emergency Caesarean section. The preliminary cause of death was reported as an acute asthma attack.
- A medical examiner case (8-95209-003G) describes a 17-year-old female smoker with a recent history of bronchitis and pharyngitis and a 1-year history of intermittent Primatene Mist use who was found collapsed. The cause of death was reported as bronchial asthma with associate focal myocardial fibrosis.

- A coroner case (no HQ number*) of a 30-year-old woman with a history of asthma describes the autopsy of a patient with a history of bronchial asthma and findings consistent with an acute asthma attack as the cause of death. Also noted are pulmonary congestion, focal pulmonary atelectasis, upper extremity needle punctures and toxicology studies positive for a cocaine metabolite and cannabinoids.
- A coroner case (HQ5150211NOV2002) of an 18-year-old woman describes her use of Primatene Mist prior to playing a soccer game during which she collapsed. The coroner indicated the probable cause of death was arrhythmia secondary to asthma.
- An HCP report (HQ4306907AUG2001) describes a case of a man of unknown age who used Primatene Mist. The HCP reported that the patient died from ischemic cardiomyopathy and subsequent myocardial infarction.
- A consumer case (HQ2276316OCT2000) describes a 43-year-old woman with a history of severe asthma and obesity who ran out of her prescription asthma inhaler. She obtained Primatene Mist and reportedly took 1 inhalation and collapsed. The reporter indicated that the medical examiner attributed the death to chronic pulmonary disease.
- A consumer case (HQ2274916OCT2000) describes a 33-year-old man who used Primatene Mist and complained that he felt unwell approximately 20 minutes later. The reporter indicated that the patient was sweating and could not catch his breath; he collapsed and appeared to be having a seizure; he lost consciousness and was incoherent upon regaining consciousness. He was coughing and wheezing and his skin was pale and his lips turned purple. He stopped breathing on the way to the hospital. The autopsy report listed the cause of death as status asthmaticus.

*maintained in Wyeth Consumer Healthcare database

- A consumer legal case (HQ4599107DEC2000) reports that a man of unknown age had a “fatal cardiac arrhythmia after using Primatene Mist.”

- A consumer legal case (HQWYE109309AUG04) describes the death of a 29-year-old woman with asthma who had used Primatene Mist regularly since age 13. The cause of death was reported as a myocardial infarction.

Summary

The databases contain 28 reports describing 33 fatal outcomes coincident with the use of Primatene Mist and Primatene Tablets. Of the cases reported by HCPs, most of the deaths are attributed to cardiac or pulmonary processes. In most cases, information potentially relevant to the causes of death such as past medical history, reason for using the Primatene products, severity of asthma, illicit drug use and concomitant medications was not provided. A direct link, therefore, between use of Primatene products and death cannot be ascertained.

Summary Table of Fatal Reports

Report Source	Date of Report or Follow-Up	MCN #	Age	Gender	Adverse Event	Concomitant Medications	Comment(s)
Literature	10/1/04	HQWYE542605OCT04	66	Unk	Intentional misuse	Unk	Pt. intentionally misused drug and overdosed.
HCP (ME)	7/19/95	8-95235-009C	32	F	Dyspnea; Death	Prenatal vitamins	Seven months pregnant; h/o chronic asthma; complained of dyspnea and used PM at 10-11pm; awoke the following morning (4am) with difficulty breathing and collapsed. In the ED, patient had no pulse or respirations. Emergency Caesarean section performed; healthy twin girls were delivered. Patient was pronounced dead at 4:49am; cause of death (prelim) acute asthma attack.
HCP (ME)	7/14/95	8-95209-003G	17	F	Cardio-respiratory arrest; Death; Asthma; Myocardial fibrosis	Zantac; Donnatal; Reglan	Smoker; recent h/o pharyngitis & bronchitis treated with Biaxin, Medrol dose pack & Maxair MDI. One year h/o intermittent PM use; found collapsed; CPR unsuccessful; ME reported: "…it is our professional opinion within a reasonable degree of medical certainty that (the patient's) unfortunate sudden & unexpected death was due to bronchial asthma with associate focal myocardial fibrosis and that the manner of death was natural. An extensive toxicological screen was essentially negative."

Summary Table of Fatal Reports

Report Source	Date of Report or Follow-Up	MCN #	Age	Gender	Adverse Event	Concomitant Medications	Comment(s)
HCP (Coroner)	4/27/92	N/A	30	F	Asthma	None reported	Per autopsy: history of asthma; findings consistent with acute asthma attack; pulmonary congestion; focal atelectasis; needle punctures antecubital fossae/wrists. Examining physician's opinion: -death resulted from an acute asthmatic attack. Cocaine and cannabinoids positive. Case initially called in by mother (4/2/92).
HCP (Coroner)	11/8/02	HQ5150211NOV2002	18	F	Arrhythmia	Unk	H/o asthma. PM used prior to playing in soccer game; patient collapsed. Autopsy showed no cause of death; probable arrhythmia secondary to asthma per coroner.
HCP (Coroner)	3/23/04	HQWYE102525MAR04	Unk	M	Road traffic accident; Blood alcohol increased	Albuterol (suspect)	Per coroner's office, pt was driving under the influence of alcohol, had auto accident and died. Uncertain if/when pt used MDI or which product used. Asking if PM would have an effect on blood alcohol level.
HCP (ME)	4/4/97	HQ2276116OCT2000	40	M	Overdose	Unk	Per the ME, pt. was found dead in his bathroom with a syringe in his right antecubital space and a canister of product was lying close to the body. It was assumed that he may have extracted epinephrine from canister and administered a lethal dose intravenously.

Summary Table of Fatal Reports

Report Source	Date of Report or Follow-Up	MCN #	Age	Gender	Adverse Event	Concomitant Medications	Comment(s)
HCP	8/7/01	HQ4306907AUG2001	Unk	M	Cardiomyopathy; Myocardial infarction	Unk	Initial information was received from the wife of the patient & follow-up information received from a physician who reported that the patient experienced ischemic cardiomyopathy with a subsequent MI.
HCP	1/3/03	HQ6062908JAN2003	Unk	F	Death	Unk	HCP reported a patient (a model) died while using the product. No further details provided.
Consumer	4/29/02	HQ2118830APR2002	54	M	Hemorrhagic stroke; Cardiac arrest	Primatene Mist & Tablets	Legal case; h/o HTN; family h/o heart disease; took Robitussin CF. PM and tablets were concomitant meds. Cerebral hemorrhage, confirmed by autopsy as the cause of death due to hypertensive and arteriosclerotic cardiovascular disease. Pt. collapsed and was found unconscious.
Consumer	9/15/97	HQ2276316OCT2000	43	F	Hyperhidrosis; Hyperventilation; Death; Asthma	Unspecified asthma MDI	H/o severe asthma; obesity; Ran out of Rx MDI and got PM from the military PX, took 1 spray and collapsed in the parking lot. According to the reporter, the ME's report noted: that the cause of death was attributed to chronic pulmonary disease and toxicology report was negative.
Consumer	3/21/97	HQ2274916OCT2000	33	M	Cardiac arrest; Apnea; syncope; Convulsion; Asthma; Hyperhidrosis	Unk	Used PM, about 20 minutes later did not feel well; sweating, dyspneaic, collapsed appeared to be having seizure; coughing, wheezing, lost consciousness, lips turned purple; stopped breathing on way to hospital. The autopsy report listed the cause of death as status asthmaticus.

Summary Table of Fatal Reports

Report Source	Date of Report or Follow-Up	MCN #	Age	Gender	Adverse Event	Concomitant Medications	Comment(s)
Consumer	8/13/02	HQ3758914AUG2002	Unk	F	Death	Unk	Information was received from a consumer that a female had died while using PM. No further details provided.
Consumer	8/13/02	HQ3805515AUG2002	Unk	Unk	Death	Unk	Consumer reported that someone had died from using the product. No further details provided.
Consumer	8/19/02	HQ3874720AUG2002	Unk	F	Death	Unk	Consumer reported that a pharmacist told him " a little girl passed away while using this product." No further details provided.
Consumer	8/21/02	HQ3949226AUG2002	Unk	Unk	Death; Palpitations	Unk	Consumer reported that a pharmacist stated that the product caused heart palpitations and "had caused 6 deaths." No further details provided.
Consumer	9/3/02	HQ4076305SEP2002	Unk	F	Death	Unk	Consumer reported that a female patient died while using product. No further details provided.
Consumer	9/17/02	HQ4287119SEP2002	Unk	F	Death	Unk	Consumer reported " a model died from using the product." No further details provided.
Consumer	8/30/95	HQ4598307DEC2000	Unk	M	Drug dependence; Apnoea; Nervousness; Tachycardia; Nonspecific reaction	Unk	Consumer reports that brother died from respiratory failure caused by excessive use of PM. Consumer reports that PM made the brother irritable & nervous and that he was addicted to it.
Consumer	8/10/95	HQ4599107DEC2000	Unk	M	Arrhythmia	Unk	Legal case. "Decedent suffered fatal cardiac arrhythmia after using Primatene Mist." No further details provided.

Summary Table of Fatal Reports

Report Source	Date of Report or Follow-Up	MCN #	Age	Gender	Adverse Event	Concomitant Medications	Comment(s)
Consumer	10/10/02	HQ4644815OCT2002	Unk	F	Completed suicide	Unk	Consumer reported that a "model killed herself on this product." No further details provided.
Consumer	8/8/02	HQ4690617OCT2002	Unk	F	Overdose	Unk	Consumer reported that a "famous model in Florida died from using the product too much." No further details provided.
Consumer	11/18/02	HQ5448621NOV2002	Unk	Unk	Intentional Misuse; Drug Abuser	Unk	Consumer read in Denver paper several months prior that 2 children OD'd on PM while attempting to get high, 1 of the children died. No further details provided.
Consumer	12/12/02	HQ5822318DEC2002	Unk	F	Asthma	Unk	Consumer reported "a girl down the street died from an asthma attack." No further details provided.
Consumer	12/16/02	HQ5848719DEC2002	Unk	M	Drug administration Error	Unk	Pharmacy clerk reported that a consumer stated "a little boy passed away after using the product incorrectly." No further details provided.
Consumer	12/20/02	HQ5907926DEC2002	Unk	M	Completed suicide	Unk	Consumer reported she had been told " a movie star's son had committed suicide using the product." No further details provided.
Consumer	8/5/04	HQWYE109309AUG04	29	F	Myocardial infarction	Unk	Legal case. Pt with asthma used PM regularly since age 13. Cause of death reported as MI.
Consumer	2/3/04	HQWYE813704FEB04	Unk	F	Death	Unk	Reporter stated a patient (smoker) died as a result of using product. No further details provided.

PRIMATENE MIST
SERIOUS ADVERSE EVENTS

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1.0 INTRODUCTION

In response to a query from Wyeth Consumer Healthcare, the Global Safety Surveillance and Epidemiology (GSSE) department has conducted a search of the Safety Surveillance System (S^3) for serious adverse events (SAEs) received coincident with administration of Primatene Mist. Specifically, a search of the database included all serious reports received from the United States, both medically confirmed and non-medically confirmed events, received by Wyeth through 31 October 2005. Additionally, a separate search of the Wyeth Consumer Healthcare database was conducted utilizing the same search criteria for those reports received prior to creation of the S^3 database.

The Primatene Mist data is summarized in tabular format and is presented as follows:

Table 1.0-1: Serious Adverse Events by System Organ Class from S^3 Database
Table 1.0-2: Serious Adverse Event Reports by Age Group and Gender from S^3 Database
Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database
Table 1.0-4: Serious Adverse Event Reports Case ID from Wyeth Consumer Healthcare Database

This data will be incorporated into a risk/benefit assessment to be presented to the Food and Drug Administration (FDA) at an Advisory Committee meeting regarding Primatene Mist and chlorofluorocarbons (CFC) scheduled for January 2006.

Table 1.0-1: Serious Adverse Events by System Organ Class (SOC) from S[3] Database

Primary SOC	Preferred Term	Outcome[a]						Total
		F	R'd	R'ing	NR	NA	Unk	
CardiacDisorders	Arrhythmia	2	-	-	-	-	-	2
	Atrial fibrillation	-	-	-	-	1	-	1
	Cardiac Arrest	1	-	-	-	-	-	1
	Cardiac Disorder	-	1	-	-	-	1	2
	Cardio-respiratory arrest	1	-	-	-	-	-	1
	Cardiomyopathy	1	-	-	-	-	-	1
	Cardiovascular Disorder	-	-	-	-	-	1	1
	Myocardial fibrosis	1	-	-	-	-	-	1
	Myocardial infarction	2	-	-	-	1	3	6
	Palpitations	-	2	-	-	-	1	3
	Tachycardia	1	1	1	-	1	-	4
Congenital, familial and genetic disorders	Congenital anomaly	-	-	-	-	-	1	1
Eye Disorders	Cataract	-	-	-	-	-	1	1
	Eye Rolling	-	1	-	-	-	-	1
Gastrointestinal disorders	Dry mouth	-	-	-	1	-	-	1
	Nausea	-	3	-	-	-	-	3
	Vomiting	-	-	1	-	-	-	1

[a] F=Fatal, R'd=Recovered/Resolved, R'ing=Recovering/Resolving, NR=Not Recovered/Not Resolved, NA=Not Provided, Unk=Unknown

Table 1.0-1: Serious Adverse Events by System Organ Class (SOC) from S[3] Database

Primary SOC	Preferred Term	Outcome[a]						Total
		F	R'd	R'ing	NR	NA	Unk	
General disorders and administration site conditions	Asthenia	-	-	1	2	-	1	4
	Chest discomfort	-	2	-	-	-	-	2
	Chest pain	-	3	-	2	-	2	7
	Condition aggravated	-	1	-	2	-	1	4
	Death	11	-	-	-	-	-	11
	Difficulty in walking	-	-	-	1	-	-	1
	Drug ineffective	-	-	-	-	2	1	3
	Drug interaction	-	-	-	-	1	-	1
	Fatigue	-	1	-	-	-	-	1
	Feeling abnormal	-	-	-	-	-	1	1
	Feeling cold	-	1	-	-	-	-	1
	Nonspecific reaction	1	-	-	-	-	2	3
	Obstruction	-	-	-	-	-	1	1
	Oral administration complication	-	-	-	-	-	1	1
	Pain	-	-	-	-	-	1	1
	Therapeutic response unexpected	-	-	-	-	-	1	1
	Unevaluable event	-	1	-	-	-	-	1
Hepatobiliary disorders	Liver disorder	-	-	-	-	-	1	1
Infections and Infestations	Rhinitis	-	-	-	-	-	1	1
Injury, poisoning and procedural complications	Accidental overdose	-	-	-	-	-	1	1
	Drug administration error	1	-	-	-	-	-	1

Table 1.0-1: Serious Adverse Events by System Organ Class (SOC) from S[3] Database

Primary SOC	Preferred Term	Outcome[a]						Total
		F	R'd	R'ing	NR	NA	Unk	
	Drug exposure during pregnancy	-	-	-	-	1	-	1
	Fall	-	-	-	-	-	1	1
	Incorrect route of drug administration	-	1	-	-	-	-	1
	Intentional misuse	1	-	-	1	-	-	2
	Intentional overdose	2	1	-	1	1	4	9
	Overdose	2	-	-	-	9	7	18
	Road traffic accident	1	-	-	-	-	-	1
Investigations	Blood alcohol increased	-	-	-	1	-	-	1
	Blood pressure increased	-	1	-	1	-	-	2
	Breath alcohol test positive	-	-	-	-	-	1	1
	False positive laboratory result	-	-	-	-	-	1	1
	Heart rate increased	-	2	-	-	-	-	2
	Heart rate irregular	-	1	-	1	-	-	2
	Weight increased	-	-	-	1	-	-	1
Musculoskeletal and connective tissue disorder	Joint stiffness	-	-	-	1	-	-	1
	Myalgia	-	-	-	-	-	1	1
	Myopathy	-	-	-	-	-	1	1
	Pain in extremity	-	-	-	1	-	-	1
Nervous system disorders	Cerebrovascular accident	-	-	-	-	-	1	1
	Convulsion	1	1	-	-	-	-	2
	Depressed level of consciousness	-	1	-	-	-	-	1
	Dizziness	-	2	1	3	-	2	8

Table 1.0-1: Serious Adverse Events by System Organ Class (SOC) from S[3] Database

Primary SOC	Preferred Term	Outcome[a]						Total
		F	R'd	R'ing	NR	NA	Unk	
	Headache	-	1	-	-	-	-	1
	Loss of consciousness	-	1	-	1	-	-	2
	Syncope	1	-	-	-	1	-	2
	Tremor	-	-	1	1	-	-	2
Psychiatric disorders	Anxiety	-	-	-	-	-	1	1
	Completed suicide	2	-	-	-	-	-	2
	Dependence	-	-	-	-	-	2	2
	Drug dependence	1	-	-	6	1	19	27
	Nervousness	1	-	-	-	-	-	1
	Panic attack	-	-	-	-	-	1	1
Renal and urinary disorders	Renal failure acute	-	-	-	-	1	-	1
Respiratory, thoracic and mediastinal disorders	Apnoea	2	-	-	-	-	-	2
	Asthma	4	-	-	1	-	-	5
	Choking	-	1	-	-	-	-	1
	Cough	-	-	-	1	-	1	2
	Dyspnoea	1	4	-	2	1	3	11
	Hyperventilation	1	-	-	-	-	-	1
	Lung disorder	-	1	-	1	-	-	2
	Pharyngeal oedema	-	1	-	-	-	-	1
	Pulmonary artery aneurysm	-	-	-	1	-	-	1
	Pulmonary thrombosis	-	-	-	1	-	-	1
	Respiratory disorder	-	-	-	-	-	1	1

Table 1.0-1: Serious Adverse Events by System Organ Class (SOC) from S[3] Database

Primary SOC	Preferred Term	Outcome[a]						Total
		F	R'd	R'ing	NR	NA	Unk	
	Respiratory tract irritation	-	1	-	-	-	1	2
	Throat tightness	-	1	-	1	-	-	2
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	-	1	-	-	2	4
Social circumstances	Drug abuser	1	1	-	-	2	6	10
Vascular disorders	Aneurysm	-	-	-	-	-	1	1
	Hypertension	-	1	-	-	-	-	1
	Pallor	-	1	-	-	-	-	1

Table 1.0-2: Serious Adverse Event Reports by Age Group & Gender from S^3 Database

	Adult	Elderly	Infant	Unknown	Total
Female	26	1	1	22	50
Male	22	8	0	17	47
Unknown	0	1	0	8	9
Total	48	10	1	47	106

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
8-95209-003G	Yes	17 Yr	Adult	Female	Fatal	- Not Provided	- Asthma - Cardio-respiratory arrest - Death - Myocardial fibrosis
8-95235-009C	Yes	32 Yr	Adult	Female	Fatal	- Not Provided	- Death - Dyspnoea
8-98216-004F	No	54 Yr	Adult	Female	Not Provided	- Not Provided	- Dyspnoea - Syncope
8-98226-002F	Yes	29 Yr	Adult	Female	Not Provided	- Not Provided	- Atrial fibrillation - Myocardial infarction - Overdose - Renal failure acute
8-99011-014X	No	21 Yr	Adult	Female	Not Provided	- Not Provided	- Drug ineffective - Tachycardia

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ0531031 AUG2000	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Aneurysm - Oral administration complication
HQ1060528 FEB2002	No	29 Yr	Adult	Female	Recovered/ Resolved	- Not Provided	- Dyspnoea - Eye rolling - Heart rate increased
HQ1642205 JUN2001	No	38 Yr	Adult	Male	Not Recovered / Not Resolved	- Asthma	- Asthenia - Difficulty in walking - Joint stiffness - Tremor
HQ1650605 APR2002	No	42 Yr	Adult	Male	Unknown	- Hypercholesterolaemia - Hypertension	- Drug dependence - Intentional overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ1793207 JUN2001	Yes	37 Yr	Adult	Female	1.Not Recovered/ Not Resolved 2.Unknown	- Drug abuser - Drug hypersensitivity - Smoker	- 1.Drug dependence - 2.Dyspnoea - Hyperhidrosis - Panic attack
HQ1844408 JUN2001	No	42 Yr	Adult	Female	Recovered / Resolved	- Asthma - Cardiac disorder - Hypertension - Systemic lupus erythematosus	- Blood pressure increased - Overdose
HQ2118206 APR2000	No	21 Yr	Adult	Female	Recovered / Resolved	- Asthma - Eczema	- Chest pain - Drug ineffective - Dyspnoea - Palpitations

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ2118506 APR2000	No	24 Yr	Adult	Female	Recovering / Resolving	- Asthma - Pregnancy	- Asthenia - Dizziness - Hyperhidrosis - Tachycardia - Tremor - Vomiting
HQ2274916 OCT2000	No	33 Yr	Adult	Male	Fatal	- Not Provided	- Apnoea - Asthma - Cardiac arrest - Convulsion - Hyperhidrosis - Syncope
HQ2276116 OCT2000	Yes	40 Yr	Adult	Male	Fatal	- Not Provided	- Overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ2276316 OCT2000	No	43 Yr	Adult	Female	Fatal	- Asthma	- Asthma - Death - Hyperhidrosis - Hyperventilation
HQ2339717 OCT2000	No	Not Provided	Not Provided	Male	Unknown	- Benign prostatic hyperplasia	- Anxiety - Asthenia - Cardiovascular disorder - Chest pain - Pain
HQ2340317 OCT2000	No	20 Yr	Adult	Female	Unknown	- Asthma	- Chest pain - Cough - Dizziness - Drug ineffective - Dyspnoea - Rhinitis

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ2349917 MAY2002	No	33 Yr	Adult	Male	Not Recovered/Not Resolved	- Asthma	- Asthma - Condition aggravated
HQ2687812 JUN2002	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Drug dependence
HQ3502926 JUL2002	No	Not Provided	Not Provided	Female	Not Provided	- Alcoholism - Hypertension	- Drug abuser
HQ3638307 AUG2002	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Drug dependence
HQ3658908 AUG2002	No	47 Yr	Adult	Female	Unknown	- Asthma	- Drug dependence
HQ3684912 AUG2002	No	58 Yr	Adult	Male	Not Provided	- Not Provided	- Drug dependence

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ3720213 AUG2002	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Drug dependence
HQ3758914 AUG2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Death
HQ3760714 AUG2002	No	17 Yr	Adult	Female	Not Recovered/ Not Resolved	- Systemic lupus erythematosus	- Drug dependence
HQ3782915 AUG2002	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Drug dependence
HQ3805515 AUG2002	No	Not Provided	Not Provided	Unknown	Fatal	- Not Provided	- Death
HQ3805915 AUG2002	No	Not Provided	Not Provided	Unknown	Unknown	- Not Provided	- Myocardial infarction - Overdose
HQ3806115 AUG2002	No	Not Provided	Not Provided	Unknown	Unknown	- Not Provided	- Drug abuser

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ3872920 AUG2002	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Drug dependence - Overdose
HQ3874720 AUG2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Death
HQ3899821 AUG2002	No	Not Provided	Not Provided	Unknown	Unknown	- Not Provided	- Drug abuser
HQ3922522 AUG2002	No	23 Yr	Adult	Male	Not Recovered/ Not Resolved	- Pneumonia	- Drug dependence - Overdose
HQ3930223 AUG2002	No	Not Provided	Not Provided	Unknown	Unknown	- Not Provided	- Cardiac disorder
HQ3948826 AUG2002	No	44 Yr	Adult	Male	Not Recovered/ Not Resolved	- Not Provided	- Chest pain - Drug dependence - Heart rate irregular - Overdose - Pain in extremity

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ3949226 AUG2002	No	Not Provided	Not Provided	Unknown	Fatal	- Not Provided	- Death - Palpitations
HQ3981628 AUG2002	No	42 Yr	Adult	Male	Unknown	- Not Provided	- Drug dependence - Liver disorder
HQ4002429 AUG2002	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Drug dependence
HQ4003029 AUG2002	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Drug dependence - Overdose
HQ4023403 SEP2002	No	Not Provided	Not Provided	Male	Unknown	- Emphysema	- Drug dependence
HQ4025803 SEP2002	No	52 Yr	Adult	Female	Unknown	- Arthritis - Asthma - Collapse of lung	- Drug dependence - Intentional overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ4076305 SEP2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Death
HQ4095506 SEP2002	No	74 Yr	Elderly	Male	Unknown	- Alcoholism - Hernia - Skin cancer - Urinary incontinence	- Drug dependence - Intentional overdose
HQ4162611 SEP2002	No	59 Yr	Adult	Male	Not Recovered/ Not Resolved	- Hypertension	- Dizziness - Drug abuser
HQ4182212 SEP2002	No	32 Yr	Adult	Female	Not Recovered/ Not Resolved	- Not Provided	- Drug dependence - Weight increased
HQ4287119 SEP2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Death

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ4287319 SEP2002	No	27 Yr	Adult	Male	Unknown	- Anxiety - Dyspnoea	- Drug dependence - Overdose
HQ4306907 AUG2001	No	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Cardiomyopathy - Myocardial infarction
HQ4461509 AUG2001	No	Not Provided	Not Provided	Female	Recovered/ Resolved	- Not Provided	- Cardiac disorder
HQ4598307 DEC2000	No	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Apnoea - Drug dependence - Nervousness - Nonspecific reaction - Tachycardia
HQ4599107 DEC2000	No	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Arrhythmia

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ4599207 DEC2000	Yes	33 Yr	Adult	Male	Unknown	- Not Provided	- Myalgia - Myopathy
HQ4644815 OCT2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Completed suicide
HQ4690617 OCT2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Overdose
HQ5150211 NOV2002	Yes	18 Yr	Adult	Female	Fatal	- Asthma	- Arrhythmia
HQ5152911 NOV2002	No	69 Yr	Elderly	Male	1.Recovered/ Resolved, 2.Unknown	- Not Provided	- 1.Headache - 2.Drug dependence - Overdose
HQ5424520 NOV2002	No	Not Provided	Not Provided	Female	Recovered/ Resolved	- Not Provided	- Convulsion - Overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ5448621 NOV2002	No	Not Provided	Not Provided	Unknown	Fatal	- Not Provided	- Drug abuser - Intentional overdose
HQ5501825 NOV2002	No	Not Provided	Not Provided	Unknown	Unknown	- Not Provided	- Drug abuser - Intentional overdose
HQ5822318 DEC2002	No	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Asthma
HQ5848719 DEC2002	No	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Drug Administration error
HQ5907926 DEC2002	No	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Completed suicide
HQ5955830 DEC2002	No	60 Yr	Adult	Male	Not Recovered/ Not Resolved	- Not Provided	- Drug dependence - Intentional overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ6062908 JAN2003	Yes	Not Provided	Not Provided	Female	Fatal	- Not Provided	- Death
HQ6200322 MAY2000	Yes	64 Yr	Elderly	Male	Unknown	- Not Provided	- Cerebrovascular accident
HQ6290022 JAN2003	No	Not Provided	Not Provided	Female	Unknown	- Back pain	- Dependence - Drug exposure during pregnancy
HQ6325723 JAN2003	Yes	44 Yr	Adult	Female	Recovered/ Resolved	- Smoker	- Throat tightness
HQ6644331 JAN2001	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Obstruction
HQ6766302 JUN2000	No	Not Provided	Not Provided	Male	Recovered/ Resolved	- Not Provided	- Choking
HQ8222706 JUL2000	Yes		Infant	Female	Unknown	- Not Provided	- Congenital anomaly

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQ9121705 DEC2001	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Myocardial infarction
HQWYE01 7814APR05	No	57 Yr	Adult	Male	Unknown	- Cardiac disorder - Cardiac pacemaker insertion - Emphysema - Hospitalization due to heart condition	- Dependence - Drug abuser - Overdose
HQWYE06 0824MAR0 4	Yes	51 Yr	Adult	Male	Recovered/ Resolved	- Blood cholesterol increased - Hypersensitivity - Migraine	- Chest discomfort - Chest pain - Dizziness - Dyspnoea - Respiratory tract irritation

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE079807MAY03	Yes	Not Provided	Not Provided	Female	Unknown	- Respiratory disorder - Smoker	- Condition aggravated - Respiratory disorder
HQWYE102525MAR04	Yes	Not Provided	Not Provided	Male	Fatal	- Not Provided	- Blood alcohol increased - Road traffic accident
HQWYE109309AUG04	No	29 Yr	Adult	Female	Fatal	- Not Provided	- Myocardial infarction
HQWYE138310AUG04	No	35 Yr	Adult	Male	Unknown	- Hypertension - "diastolic number is usually very high"	- Drug abuser - Overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE144510OCT03	No	66 Yr	Elderly	Male	Not Recovered/ Not Resolved	- Not Provided	- Dry mouth - Intentional misuse - Intentional overdose - Throat tightness
HQWYE157518AUG03	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Cataract
HQWYE173007JAN04	No	69 Yr	Elderly	Male	Unknown	- Leukaemia in remission - Prostatic operation - Renal impairment	- Breath alcohol test positive - False positive laboratory result - Overdose - Respiratory tract irritation

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE350315FEB05	No	20 Yr	Adult	Male	Recovered/ Resolved	- Asthma - Attention deficit/hyper-activity disorder	- Lung disorder
HQWYE386513FEB03	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Drug dependence - Dyspnoea - Overdose
HQWYE392217FEB05	No	38 Yr	Adult	Female	Not Recovered/ Not Resolved	- Asthma - Smoker	- Condition aggravated - Dyspnoea - Lung disorder

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE463615NOV04	No	79 Yr	Elderly	Male	Unknown	- Diabetes mellitus - Hypertension - Obesity - Poor peripheral circulation - Skin ulcer	- Drug abuser - Overdose
HQWYE487415SEP05	No	70 Yr	Elderly	Female	Recovered/ Resolved	- Not Provided	- Heart rate increased
HQWYE489009DEC03	No	39 Yr	Adult	Female	Not Recovered/ Not Resolved	- Not Provided	- Asthenia - Dizziness - Dyspnoea - Pulmonary artery aneurysm - Pulmonary thrombosis

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE536721JUN04	No	Not Provided	Not Provided	Female	Unknown	- Not Provided	- Nonspecific reaction
HQWYE542605OCT04	Yes	66 Yr	Elderly	Unknown	Fatal	- Not Provided	- Intentional misuse - Intentional overdose
HQWYE592209SEP03	No	24 Yr	Adult	Female	Recovered/ Resolved	- Anxiety - Anxiety disorder	- Depressed level of consciousness - Feeling cold - Heart rate irregular - Pallor - Unevaluable event
HQWYE592429JUL05	Yes	34 Yr	Adult	Male	Recovered/ Resolved	- Asthma - Depression - Polysubstance abuse	- Chest pain - Drug abuser - Incorrect route of drug administration - Intentional overdose

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE595409MAY05	No	24 Yr	Adult	Male	Not Recovered/ Not Resolved	- Nasopharyngitis - Seasonal allergy	- Dizziness - Loss of consciousness
HQWYE636423JUN05	No	44 Yr	Adult	Female	Recovered/ Resolved	- Asthma	- Pharyngeal oedema
HQWYE644427AUG04	No	67 Yr	Elderly	Male	Not Recovered/ Not Resolved	- Hypertension	- Blood pressure increased
HQWYE650709MAR04	No	Not Provided	Not Provided	Male	Unknown	- Not provided	- Nonspecific reaction

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE690826FEB03	Yes	24 Yr	Adult	Male	Recovered/ Resolved	- Asthma	- Chest discomfort - Dizziness - Drug interaction - Fatigue - Hypertension - Loss of consciousness - Nausea - Tachycardia
HQWYE699927FEB03	No	32 Yr	Adult	Female	1.Not Recovered/ Not Resolved, 2.Recovered/ Resolved	- Overweight	- 1.Chest pain & Cough - 2.Nausea & Palpitations
HQWYE732913MAY05	No	89 Yr	Elderly	Male	Unknown	- Not Provided	- Myocardial infarction - Therapeutic response unexpected

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE780221JAN05	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Drug dependence
HQWYE793919DEC03	No	30 Yr	Adult	Female	Recovered/ Resolved	- Asthma	- Nausea
HQWYE798306NOV03	No	Not Provided	Adult	Female	Unknown	- Not Provided	- Accidental overdose - Dizziness - Fall - Feeling abnormal
HQWYE813704FEB04	No	Not Provided	Not Provided	Female	Fatal	- Smoker	- Death
HQWYE946709SEP04	No	Not Provided	Not Provided	Male	Unknown	- Not Provided	- Drug dependence - Overdose
HQWYE970318MAR04	No	29 Yr	Adult	Male	Recovered/ Resolved	- Not Provided	- Condition aggravated - Dyspnoea

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S[3] Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term
HQWYE996031DEC03	No	62 Yr	Adult	Male	Unknown	- Anticoagulant therapy - Blood cholesterol increased - Blood triglycerides increased - Bone density decreased - Bronchitis - Chest pain - Dry skin - Emphysema - Esophageal ulcer - Flatulence - Fluid retention - Gastric irritation - Ulcer - Hypersensitivity - Hypertension - Lower respiratory tract infection - Pulmonary congestion - Pain	- Drug dependence

Table 1.0-3: Serious Adverse Event Reports by Case Identification (ID) from S^3 Database

Case ID	Medically Confirmed	Age	Age Group	Gender	Outcome	Medical History	Preferred Term

Table 1.0-4: Serious Adverse Event Reports by Case Identification (ID) from Wyeth Consumer Healthcare Database (Received prior to creation of S^3 Database)

Case ID	Medically Confirmed	Age	Gender	Event Outcome	Medical History	Adverse Event
90-002P	No	61 Yr	Female	Recovered	"Silent" heart attack	Shortness of Breath
90-003P	Yes	60+ Yr	Female	Unknown	NA	Palpitation Chest pain Overdose
90-006P	No	20 Yr	Female	Not recovered	Drug exposure during pregnancy	Phocomelia-small for gestational age infant Congenital anomalies Drug exposure during pregnancy
90-010P	No	41 Yr	Male	Recovered	Asthma	Accidental ingestion of plastic cap
90-012P	No	38 Yr	Male	Recovered	Allergy to horses and anything furry	Edema peripheral Pneumonia

Table 1.0-4: Serious Adverse Event Reports by Case Identification (ID) from Wyeth Consumer Healthcare Database (Received prior to creation of S^3 Database)

Case ID	Medically Confirmed	Age	Gender	Event Outcome	Medical History	Adverse Event
90-013P	Yes	19 Yr	Male	Recovered	Mild asthma	Convulsions Tachycardia Pyrexia
90-014P	Yes	Not Provided	Female	Unknown	Hypertension Arthritis	Cardiomyopathy secondary to acute hypertension
93-027P	No	73 Yr	Male	Recovered	High blood pressure Low blood count Rapid heart beat	Dyspnea
92-005P	No	30 Yr	Female	Fatal	Chronic asthmatic condition Police found white powder substance resembling cocaine at scene Large amount of marijuana at scene Possible fresh needle punctures noted	Death due to sudden acute asthma

Table 1.0-4: Serious Adverse Event Reports by Case Identification (ID) from Wyeth Consumer Healthcare Database (Received prior to creation of S^3 Database)

Case ID	Medically Confirmed	Age	Gender	Event Outcome	Medical History	Adverse Event
93-001P	No	61 Yr	Male	Recovered	Asthmas history	Prostate disease
94-008	No	65 Yr	Male	Recovered	Asthma	Drug ineffective
94-017	No	32 Yr	Female	Recovered	Allergies to: Penicillin and dust Asthma	Severe abdominal pain Deep sweats Paleness Stinging in back of throat Bad bite on tongue
94-2910-022	No	61 Yr	Male	Recovered	Heavy smoker Primatene Mist abuse Acute emphysema Acute bronchitis	Increased sluggishness Difficulty in moving
94-2910-023	No	39 Yr	Female	Recovered	Asthma	Worsened asthma attack
95-015	Yes	33 Yr	Male	Not Recovered	Exercise induced asthma Prior ibuprofen use Prior Albuterol inhaler use	Rhabdomyolysis

Table 1.0-4: Serious Adverse Event Reports by Case Identification (ID) from Wyeth Consumer Healthcare Database (Received prior to creation of S^3 Database)

Case ID	Medically Confirmed	Age	Gender	Event Outcome	Medical History	Adverse Event

APPENDIX 5 – AAPCC REVIEW

In preparation for the Advisory Committee Meeting, Wyeth Consumer Healthcare requested exposure data from the American Association of Poison Control Centers (AAPCC). Since Wyeth Consumer Healthcare historically has marketed two brands of metered dose inhaler products, (Primatene ® and Bronitin ®), AAPCC was requested to search their database for all reports associated with the use of inhaled epinephrine for the time period January 1, 1988 to December 31, 2004.

For the seventeen-year period reviewed, a total of 431 exposures were reported to AAPCC. Of these, the most frequently reported outcome was designated by AAPCC as "Minor effect" (25% of all cases) followed by "Not followed" (22%) and "No Effect" (22%). As shown in Table 1, three fatality reports were received by AAPCC and there were three cases designated with an outcome of "Major Effect".

Table 1 Outcome summary of exposures received by AAPCC

AAPCC designated Outcome	Frequency	Proportion of all exposures (%)
Death	3	0.5
Major Effect	3	0.5
Moderate Effect	41	9.5
Minor Effect	109	25.3
No Effect	94	21.8
Not Followed, judged as nontoxic exposure (clinical effects not expected)	22	5.1
Not Followed, minimal clinical effects possible (no more than minor effect possible	95	22.0
Unable to follow, judged as a potentially toxic exposure	34	7.9
Unrelated effect, the exposure was probably not responsible for the effect(s)	32	7.4

Major Effect: The patient exhibited signs or symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

Moderate Effect: the patient exhibited signs or symptoms as a result of the exposure which were more pronounced, more prolonged, or more of a systematic nature than minor symptoms.

Minor Effect: The patient exhibited some signs or symptoms as a result of the exposure, but they were minimally bothersome to the patient.

Table 2 shows the distribution of exposures according to year. The greatest number of exposures was recorded in 1988 and in 1994, the fewest number of exposures were recorded. For 1990, no exposures were recorded. Between 2005 and 2005 the average number of exposures recorded by AAPCC was 55.6.

Table 2. Exposures according to reporting year

1988	1989	1990	1991	1992	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
71	19	0	8	6	4	8	11	10	6	10	52	55	59	56	56

Appendix 6 - Literature Search Results

The following table summarizes the results obtained from the comprehensive literature search described in section V.A.5 of this background document. The search resulted in 21 clinical trials. These were broken down by route of administration as follows: metered-dose inhalers (n=4), nebulizer (n=6), subcutaneous injection (n=4). In addition seven clinical trials included the use of epinephrine for acute bronchiolitis which may be a clinical model symptomatically similar to asthma.

The 14 clinical trials of epinephrine in asthma indicate that this drug is effective in the management of this condition and that the preferred route of administration is via inhalation which reduces the incidence of side effects.

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Metered-Dose Studies		
Pinnas, 1991	DB, CO, PC, R 12 (6M/6F); all with moderate to severe asthma; mean age 33 yrs (19-57 yrs) 2 inhalation of EPI (0.2 mg/inh) one minute apart, followed in 15 min by THE (130 mg) with EPH (24 mg) versus 2 inhalations of MET (0.65 mg/inh), one minute apart versus PBO inhaler and tablets.	Greater increases in FEV_1 were registered by patients receiving EPI than those receiving MET or PBO, and significantly more patients showed a faster onset of bronchodilator action while receiving EPI than MET ($p<0.05$). Compared with inhaled MET, inhaled EPI followed in 15 min by a THE-EPH tablet had a significantly earlier onset, longer duration of action, numerically greater peak effect, and patient preference. Because aerosols require a relatively small dose of drug to provide a therapeutic effect, unwanted systemic absorption of the drug and adverse effects are minimized. All three treatment groups had a similar incidence of AEs.

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Riding, 1969	Comparison of the bronchodilator and cardiac actions of 5 commercially available aerosols used in asthma 21 (15M/6F) asthmatic in-patients; mean age 42.5 yrs (13-68) Medihaler Isoforte: ISO sulphate 1000 µg Medihaler Bron: ISO sulphate 500 µg and ATR methonitrate 200 µg Medihaler Epi: adrenaline acid tartrate 700 µg Alupent: orciprenaline sulphate 1500 µg Ventolin: salbutamol 200 µg	The maximal improvement with EPI occurred in 5 min but was not evident at 30 min. Of 21 patients, 9 showed a small improvement (followed by rebound bronchoconstriction in 30 min), 7 showed variable improvement for ≥1 hr and 5 had no improvement. EPI produced a slight fall in heart rate. Ventolin was the aerosol of choice; Alupent and Medihaler Epi were significantly less effective.
Pliss, 1981	DB, R, PC comparison of aerosol versus injected EPI in asthma 25 ER patients (5M/20F) presenting with acute asthma mean age: 28 yrs (17 to 47 yrs) Regimen 1: 0.3 cc 1:1,000 EPI sc at 0, 20, and 40 min (total: .90 mg EPI) plus PBO inhaler at designated times Regimen 2: 0.3 cc sc saline plus EPI aerosol given as single puff (0.16 mg EPI per base puff) at 0,10,20,30,40, and 50 min (total 0.96 mg EPI)	In patients with mild to moderate asthma (PEFR >120), injected and inhaled EPI were of equal efficacy with the aerosol producing fewer side effects ($p<0.001$). There was no significant difference between the two groups with respect to changes in blood pressure, pulse rate, or respiratory rate

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Dauphinee, 1994 **(WM-632)**	DB, R, CO, PC 24 mild to moderate asthmatics [screening FEV_1 64.5 ± 11.1% pred.] mean age 37.4 yrs Primatene Mist delivering 0.3 mg EPI bitartrate (0.16 mg EPI base) per inhalation compared to an identical PBO inhaler	At 15 sec after 1 inhalation, 11/24 subjects receiving EPI and only 1/23 receiving PBO exhibited significant improvement in FEV_1. Clinically significant improvement was defined as an increase of ≥15% in FEV_1 above baseline; with 2 inhalations administered 1 minute apart, average time to peak bronchodilation was < 10 minutes. Mean absolute (and %) increases in FEV_1 at 15 sec after inhalation were 390 ± 60 mL (16.8 ± 2.6%) and –120 ± 7 mL (-6.1 ± 2.9%) for EPI and PBO, respectively [p <0.0001] Safety results were not provided.
Nebulizer Studies		
Kjellman, 1980	Comparative trial between racemic EPI and SAL 10 children aged 7-16 yrs (mean: 12 yrs) with stable bronchial obstruction and FEV_1 <70% predicted SAL: 0.15 mg/kg of a 5 mg/mL diluted to 4 mL. EPI: 0.04 mL/kg (0.0 mg/kg) On two consecutive days	Five of the 8 children reached FEV_1 values within normal range after the first inhalation of EPI; the corresponding figure for SAL is four out of 8 children. The effects of the two drugs do not differ significantly. "We conclude that nebulized racemic epinephrine gives a good bronchodilatory effect in children with bronchial asthma and that the side effects seem small." There were no significant changes in heart rate and diastolic pressure. A small but significant increase in mean systolic pressure (+7 mmHg) occurred 5 min after inhalation of EPI; the changes were not significant at 30 and 150 min. Three children had a sore throat after EPI inhalation and 2 of these children became pale immediately following the inhalation.

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Williams, 1994	R, DB, PC, CO Study to compare effect of drugs on cardiorespirtory parameters Six (6) outpatients with chronic stable asthma; 4M/2F(37-67 yrs) Drugs were administered via nebulizer once daily for 3 days: SAL 5 mg EPI 5 mg PBO	There was an increase in FEV_1 34 minutes after EPI and SAL compared to PBO and this was greater after SAL (41%) than EPI (18%). No changes occurred in blood pressure after any of the treatments. Both active drugs caused a significant increase in heart rate. Ventricular arrhythmias can occur in some patients on either active treatment (EPI: n=1; SAL:n=2).
Coupe, 1987	R, DB, CO 18 patients with acute severe asthma 11M/7F EPI: mean age: 46.7 yrs SAL: mean age 44.2 yrs Drugs were administered via nebulizer EPI (n=10): 1 mg SAL (n=8): 2.5 mg	There were no differences between the increase in PEF at 5 min after EPI (mean: 99 ± 20.5 L/min) or after SAL (119 ± 22.7 L/min). "These results suggest that nebulised adrenaline is as effective as a nebulised β-agonist in acute asthma and is without significant side effects." There was no change in blood pressure after EPI or SAL. Heart rate fell by an average of 8 beats/min after EPI and SAL
Abroug, 1995	R, DB 22 acute severe asthmatic patients (10M/12F) attending an ER; mean age: 33 yrs EPI (11): 2 mg over 10 min SAL (11): 5 mg over 10 min	PEF increased from 85 ± 38 L/min to 120 ± 45 L/min ($p<0.001$) with EPI and from 107 ± 28 L/min to 145 ± 19 L/min ($p<0.001$) with SAL. "After a single dose, nebulized adrenaline (2 mg) proved as effective and safe as salbutamol (5 mg) in acute severe asthma." Tolerance of both drugs was good with no side effects observed in either group.

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Zeggwagh, 2002	R, C 44 patients (31F/13M) 35 ± 11 yrs with acute severe asthma presenting to ER SAL (n=22) 10 mg/h^{-1} for 2 hrs then 5 mg q4h EPI (n=22) 6 mg/h^{-1} for 2 hrs then 3 mg q4h	During first 8 hrs of treatment PEF improved in both groups; this significant improvement began in 30 min in the EPI group and within 1 hr in the SAL group. PaO_2 increased in both groups. No additional bronchodilator therapy was required in either group. Systolic pressure and heart rate significantly decreased from baseline in both groups (no significant difference between the treatment groups). Authors noted inhalation could reduce side effects seen with systemic EPI.)
Adoun, 2004	R, DB, CO 38 (17M/21F) admitted with severe acute asthma Average age 34.5 yrs Each patient received TER 5 mg and EPI 3 mg via nebulizer for 20 min.	**First nebulization results**:Fourteen (78%) of the 18 patients who received EPI first were markedly or significantly improved compared to 11 (55%) of the 20 patients who received TER first (NS). No rise in SAP or heart rate occurred. **Second nebulization results**: After the first nebulization, 13 patients were not improved. The second nebulization led to a subjective improvement in 4 of those 13 patients. Among the 4 of 18 who were not improved with initial EPI, only one subsequently improved with TER. Three of the 9 patients who were not improved by TER initially improved with EPI. There were no significant changes in SAP or heart rate or PEF between the end of the first and the end of the second nebulization regardless of the sequence of administration. This study confirms that EPI nebulization in patients with acute severe asthma is well tolerated and at least as effective as TER nebulization.
Subcutaneous Injection Studies		

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Ben-Zvi, 1982	R, SB 50 ER patients (21M/29F) with acute asthma between ages of 12 and 20; average age in each group was about 15 yrs **Regimen 1**: FEN 0.5 mL (2.5 mg) of 0.5% solution diluted with 1.5 mL of saline delivered by nebulizer for 5-8 minutes. **Regimen 2**: EPI 0.01 mg/kg (maximum 0.3 mg) was injected sc and was followed 25 min later by Sus-Phrine 0.025 mg/kg (maximum 0.75 mg) injected sc. **Sus-Phrine:** provides 20% or 0.005 mg/kg in the form of standard EPI solution and 80% or 0.02 mg/kg in the form of aqueous suspension that is absorbed slowly over 6-8 hrs.	Both groups responded within 10 minutes and peak improvement was reached within 1 hr. Results demonstrated that an inhaled $\beta_2$agonist is effective in the initial treatment of acute asthma in children, regardless of severity and avoids the need for injections. There were no significant differences in systolic and diastolic pressure between the two groups during the study.
Quadrel, 1995	R 154 (55M/99F) moderate to severe asthmatic patients 18 to 50 yrs (mean age ~ 29 yrs) who presented to paramedics with shortness of breath and wheezing **Group 1:** EPI sc 0.3 mg 1:1,000 solution (n=53) **Group 2:** Nebulized MET 2.5 mg in 3 mL saline solution (n=49) **Group 3:** EPI sc 0.3 mg 1:1,000 solution + nebulized MET 2.5 mg in 3 mL saline solution (n=52)	Nebulized MET is as effective as EPI sc in the pre-hospital treatment of adult patients with acute asthma. Pre-hospital treatment of asthma by paramedics may influence the outcome (e.g., mortality, need for inpatient admission). "We believe it is reasonable to initiate treatment in the field. Most of the patients in our study had statistically significant increases in PEFR and improvement in symptoms by the time of arrival at the ED. Earlier treatment of acute asthma may relieve some of the burden in overcrowded EDs by decreasing length of stay and may help in determining the course of subsequent ED care."

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Heilborn, 1986	Comparison of subcutaneous injection and high-dose inhalation of EPI – implications for self-treatment to prevent anaphylaxis 12 healthy subjects (9F/3M) aged 25 to 54 yrs (mean = 38 yrs) Plasma concentrations of EPI were determined in healthy subjects administered EPI either sc (0.5 mg) or by inhalation (1.5 to 4.5 mg (10 to 30 inhalations from a metered-dose aerosol).	Individual maximal plasma levels for EPI were 4.65 ± 1.09 (0.74-8.31) nmol/L attained n 5 to 120 min after injection. After 10 inhalations of EPI, plasma levels were 2.72 ± 0.84 (0.75 to 5.67) nmol/L within 5 min and 20 inhalations resulted in 7.19 ± 1.78 (2.10 to 13.83) nmol/L. "Our results indicate that inhalation of 2 to 3 mg of epinephrine produces rapid increases of epinephrine concentrations in plasma to levels that have previously been demonstrated to counteract bronchoconstriction induced by inhaled allergen to subjects with asthma." "Apart from the absorption being more rapid, the locally high concentrations of epinephrine in the airways should be advantageous, since bronchoconstriction is one of the life-threatening phenomena of the anaphylactic reaction. The route of administration is also simple for the patient."
Sharma, 2001	R 50 asthmatic children aged 6 to 14 yrs. **Group I** (n=25): EPI sc 0.01 mL/kg dose of 1:1000 (1 mg/mL) to a maximum of 0.3 mL to be repeated twice at 20-minute intervals **Group II** (n=25): SAL nebulized for 10 minutes with 0.03 mL/kg/dose (150 µg/kg/dose) of 0.5% solution to a maximum of 1 mL (5.0 mg) per dose diluted in saline to a volume of 3 mL. The same dose was repeated twice at 20-minute intervals	Both groups had a comparable mean increase in PEFR % (Group I: 27.7 ± 0.7; Group II: 28.8 ± 0.06, p>0.05). In both groups clinical improvement continued for up to 4 hrs after treatment was begun. At 30 min, EPI caused a significant increase in heart rate and systolic pressure as compared to SAL; thereafter, the heart rates and systolic blood pressure readings for both groups were comparable Diastolic readings were similar in both treatment groups throughout the study. "Subcutaneous epinephrine can be safely used if nebulizers are not available."
Bronchiolitis Studies		
Hartling, 2003	Meta-analysis of 14 RCT evaluating the efficacy of EPI for treatment of acute viral bronchiolitis	Some evidence that EPI (nebulized) may offer some clinical benefit and EPI is more effective than PBO and ALB

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Reijonen, 1995	R, DB, PC 100 consecutive infants < 24 mo for acute bronchiolitis 2 inhalations of EPI (0.9 mg/kg) followed by saline (n=24) or 2 inhalations of SAL (0.15 mg/kg) followed by saline (n=27) or Saline followed by EPI (n=24) or Saline followed by ALB (n=25)	EPI but not SAL given as first inhalation improved respiratory assessment change score; EPI was better than SAL at 15 min. Both drugs were safe. EPI reduces bronchial mucosal edema
Lodrup, 1001 (abstract)	Open Infants 6-18 mo 7 with acute bronchiolitis and 3 with recurrent bronchopulmonary obstruction after bronchiolitis Dose not specified	Respiratory rate fell significantly as did clinical obstruction score; % volume and % time to peak tidal expiratory flow (PTEF) increased significantly as did Tidal Expiratory Flow 25/PTEF. "The changes found in this study demonstrates the effect of inhaled racemic epinephrine on infants with acute BPO objectively as well as clinically."
Rusconi, 1996 (letter to editor)	Pilot study 9 infants 1.5 to 13 mo 0.5 mg/kg up to a maximum of 5 mg of 1:1000 L EPI by nebulizer	At 15 min, the respiratory distress score improved significantly in all infants. A decrease in oxygen saturation was observed in 3 infants.
Lenney, 1978	Inpatient study of babies recovering from bronchiolitis with symptoms 21 (13M/8F) 2-17 mo Phenylephrine 2 mL 0.25% EPI 2 mL 0.4% via nebulizer	No clinical improvement observed with either treatment
Menon, 1995	R, DB 20 EPI 21 SAL 0.3 mL of a 5 mg/mL solution of SAL 3 mL of a 1:1000 EPI solution (3 mg)	EPI more effective than SAL in acute bronchiolitis and as safe. This was concluded from reduced admission rates and improved oxygen saturation at 60 min, a lower heart rate at 90 min, and faster discharge from hospital

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

Author, Year	Study Type/Subjects/Treatments	Results/Comments
Sanchez, 1993	DB, R, CO 24 (mean age 4.6 mo) 0.03 mL/kg SAL 0.1 mL/kg EPI	At 30 min, EPI showed significant improvement compared with baseline not seen with SAL. Only 13 patients had a decrease in clinical score after SAL compared with 20 on EPI. While both decreased respiratory rate, it was greater after EPI. There was a significant decrease in inspiratory, expiratory and total pulmonary resistance after EPI compared with baseline but no change with SAL No significant effect on heart rate or SaO_2. Investigators concluded that EPI is superior to SAL.

Abbreviations:
AE - adverse event; ALB - albuterol; ATR - atropine; CO - cross-over; DB - double-blind;
ED/ER - emergency department/ emergency room; EPH - ephedrine; EPI - epinephrine; FEN – fenoterol;
FEV - forced expiratory volume; ISO - isoprenaline; MET - metaproterenol; PBO - placebo; PC - placebo-controlled;
PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
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PEFR/PEF - peak expiratory flow rate; RCT - randomized controlled clinical trial; SAL - salbutamol; SC - subcutaneous;
TER - terbutaline; THE - theophylline

APPENDIX 7: OTC EPINEPHRINE MDI LABELING

The labeling below for OTC Epinephrine was revised in late 2005 to reflect the changes proposed in the July 13 2005 Tentative Final Monograph for Bronchodilators. The website screenshots reflect the labeling in effect prior to July 2005, and are in the process of being updated.

Drug Facts

Active ingredient (in each inhalation)	Purpose
Epinephrine 0.22 mg	Bronchodilator

Uses

■ for temporary relief of occasional symptoms of mild asthma:
■ wheezing ■ tightness of chest ■ shortness of breath

Warnings

Asthma alert: Because asthma can be life threatening, see a doctor if you

■ are not better in 20 minutes
■ get worse
■ need 12 inhalations in any day
■ use more than 9 inhalations a day for more than 3 days a week
■ have more than 2 asthma attacks in a week

For inhalation only

Do not use

■ unless a doctor said you have asthma
■ if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

■ ever been hospitalized for asthma ■ heart disease ■ high blood pressure ■ diabetes
■ thyroid disease ■ seizures ■ narrow angle glaucoma ■ a psychiatric or emotional condition
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are

■ taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
■ taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

When using this product

■ **increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack and stroke. Your risk may increase if you take more frequently or more than the recommended dose**.
■ nervousness, sleeplessness, rapid heart beat, tremor, and seizure may occur. If these symptoms persist or get worse, consult a doctor right away.
■ avoid caffeine-containing foods or beverages.
■ avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect.
■ do not puncture or throw into incinerator. Contents under pressure.
■ do not use or store near open flame or heat above 120°F (49°C). May cause bursting.

Contains CFC 12, 114, substances which harm public health and environment by destroying ozone in the upper atmosphere.

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

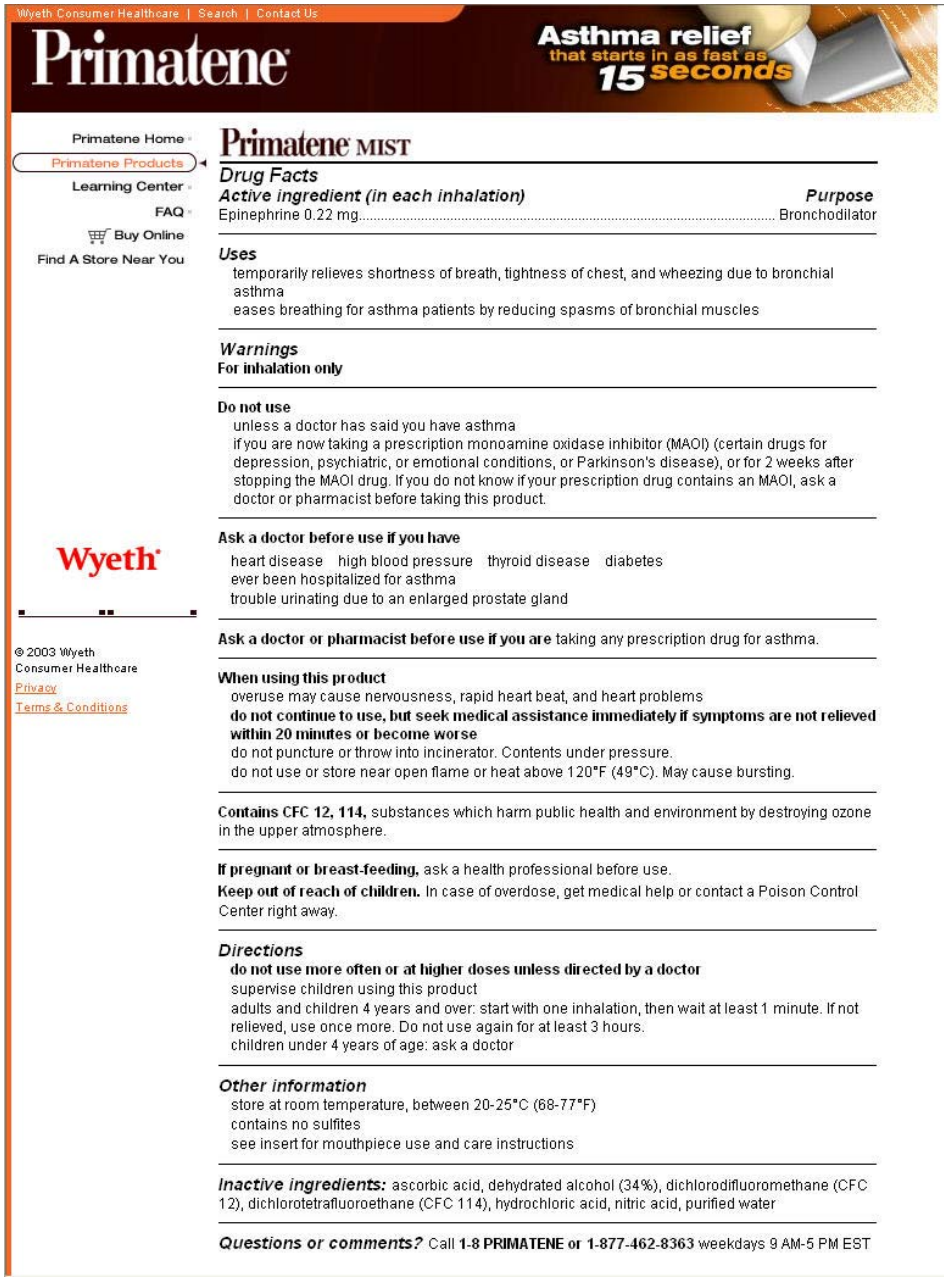
Directions

■ **do not exceed dosage**
■ supervise children using this product
■ adults and children 4 years and over: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours.

■ children under 4 years of age: ask a doctor
Other information ■ store at room temperature, between 20-25°C (68-77°F) ■ contains no sulfites ■ see insert for mouthpiece use and care instructions
Inactive ingredients ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water
Questions or comments? call **1- 8 PRIMATENE or 1-877-462-8363** weekdays 9 AM-5 PM EST **www.Primatene.com**

Website Screenshots

www.primatene.com



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Drug Facts

Active ingredient (in each inhalation)	Purpose
Epinephrine 0.22 mg	Bronchodilator

Uses

temporarily relieves shortness of breath, tightness of chest, and wheezing due to bronchial asthma
eases breathing for asthma patients by reducing spasms of bronchial muscles

Warnings

For inhalation only

Do not use

unless a doctor has said you have asthma
if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

heart disease high blood pressure thyroid disease diabetes
ever been hospitalized for asthma
trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking any prescription drug for asthma.

When using this product

overuse may cause nervousness, rapid heart beat, and heart problems
do not continue to use, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse
do not puncture or throw into incinerator. Contents under pressure.
do not use or store near open flame or heat above 120°F (49°C). May cause bursting.

Contains CFC 12, 114, substances which harm public health and environment by destroying ozone in the upper atmosphere.

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

do not use more often or at higher doses unless directed by a doctor
supervise children using this product
adults and children 4 years and over: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours.
children under 4 years of age: ask a doctor

Other information

store at room temperature, between 20-25°C (68-77°F)
contains no sulfites
see insert for mouthpiece use and care instructions

Inactive ingredients: ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water

Questions or comments? Call **1-8 PRIMATENE** or **1-877-462-8363** weekdays 9 AM-5 PM EST

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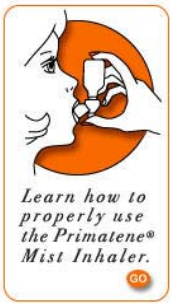

Controlling Asthma

ASTHMA IS A SERIOUS DISEASE THAT AFFECTS THE WAY YOU BREATHE, AND SHOULD BE DIAGNOSED BY A PHYSICIAN.

Coping with asthma can be difficult and frightening, especially if emergency care is needed. Asthma sufferers may have concerns about medications, the symptoms they treat and their proper use. Asthmatics and their families need to be informed about when to see a doctor for diagnosis and treatment, how to best treat asthma at home, how to prevent asthma episodes, and how to monitor physical activities. In addition, parents of asthmatic children need to be able to communicate effectively with their child's doctor, teachers, principal, and other school personnel.

ASTHMA CAN BE CONTROLLED
Managing your asthma can help you do the following:

- Reduce asthma symptoms such as coughing, wheezing or shortness of breath at night the early morning or after exertion
- Reduce the number of asthma episodes or attacks
- Prevent emergency visits to doctors and hospitals
- Reduce the need for quick-relief therapy
- Participate in physical activity and exercise without problems
- Reduce side effects from medications

Back to index

Wyeth

Asthma Triggers

LEARN WHAT TRIGGERS ASTHMA

Asthmatics have overly sensitive air passages. Common things that cause little or no trouble for most of us can leave people with asthma struggling for breath. Substances or conditions that bring on asthma attacks in certain people are called asthma triggers. Knowing what they are can help you keep asthma attacks from starting. There are two types of common asthma triggers:

A. Allergic triggers: Allergens (things that cause allergic reactions) most often trigger asthma symptoms by entering the lungs as you breathe. An asthmatic person may be allergic to one or more common allergens found in the environment.

The following particles are allergens that can be in the air:

- Indoor or outdoor molds, pollen
- Animal dander (flakes from the skin, hair, or feathers of any warm-blooded pet, including dogs, cats, birds, rodents, and horses)
- Dog hair and saliva
- Cat hair, saliva, and urine
- Dust mite particles (from microscopic insects present in house dust)
- Cockroach particles

ENVIRONMENTAL ELEMENTS
Plants, pollen, household dust, mold

ANIMALS
Dander, hair, saliva, and urine

DUST MITE PARTICLES
From microscopic insects present in house dust

ROACHES
Roach particles are a very potent allergen

FOOD ADDITIVES
Sulfites used as a preservative in some foods and beverages, such as olives and wine

CERTAIN MEDICATIONS
For example, penicillin or aspirin

Some allergies are easy to identify, like cat dander and pollen from flowers; others are harder to identify, such as house dust. Your physician can identify possible allergic triggers by asking detailed questions or through skin testing.

B. Non-allergic triggers: These have nothing to do with allergies, but cause the same airway changes as allergic triggers (i.e., airway swelling, mucus increase, and airway narrowing).

Materials (irritants) in the air:

- Tobacco smoke
- Wood smoke, pine odors
- Room deodorizers, fresh paint, household cleaning products, cooking odors, perfumes and cosmetics
- Chemical fumes, outdoor air pollution (smog, exhaust from cars and buses, smoke from factories and power plants), natural gas, propane or kerosene
- Heating units (using gas, wood, coal or kerosene)
- Respiratory infections—common colds, the flu, or sinus infections
- Exercise
- Cold air or sudden changes in weather/air temperature-cooling, storm fronts, high humidity

ENVIRONMENTAL TRIGGERS

Discuss with your doctor how to identify the asthma triggers that affect you, and determine which actions are going to be most helpful in reducing your asthma symptoms.

C. Actions that can help remove or avoid some asthma triggers:

- Cigarette smoking: Avoid cigarette smoke, especially in the home.
- Strong odors and sprays: Avoid perfumes and perfumed cosmetics, room deodorizers, and household cleaning products whenever possible. Do not stay in a house that is being painted (allow enough time for the paint to dry).
- Colds and infections: Get rest, eat a balanced diet, and exercise regularly. Avoid people with colds or the flu. Discuss flu vaccines with your doctor. Don't take over-the-counter cold medicines before checking with your doctor.
- Pets: The elimination of animal dander by removing dogs and cats from the home is desirable. If this is not possible, keep the bedroom free of pets.
- Molds: Reduce exposure to molds or mildew with good ventilation and by reducing humidity. Use humidifiers only when a "croupy" cough (barking, dry cough caused by infections of the upper airways) is present.
- Dust: If there is sensitivity to dust mites, mattresses and pillows should be encased in plastic covers (or wash the pillow once a week, every week). Wash bed covers, clothes, and stuffed toys once a week in hot water. Avoid sleeping or lying on upholstered furniture. Avoid using a vacuum cleaner or leave the room while it is being vacuumed. Remove carpets from the bedroom.
- Insects: Control of cockroach infestations is important when there is sensitivity to these pests.
- Weather: Dress warmly in cold weather and on windy days, pulling a turtleneck over your nose. Wear a scarf over the mouth and nose in cold weather.
- Outdoor pollens and molds: Stay indoors at midday and during the afternoon when the pollen count is high. If possible, use air conditioning. Keep windows closed during pollen and mold seasons. Avoid mold sources (wet leaves, garden debris).
- Exercise: Discuss with your doctor a medication plan that allows physical activity without symptoms. Take prescribed medications before exercising. Warm up before doing exercise and cool down afterwards.

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Warning Signs

Predicting an asthma episode is not the same for everyone, and early-warning signs may change from episode to episode. Make sure you follow an Asthma Action Plan prepared by your doctor as soon as warning signs develop. These may include:

- A drop in your peak-flow reading (earliest warning sign!)
- A chronic cough, especially at night
- Difficult or rapid breathing
- Chest tightness or discomfort
- Running out of breath more easily than usual
- Fatigue
- Wheezing
- Feeling that the head is stuffed up
- Headache
- Fever
- Restlessness
- A runny nose
- A change in the color of the face
- Dark circles under the eyes
- Other symptoms identified by you and your physician

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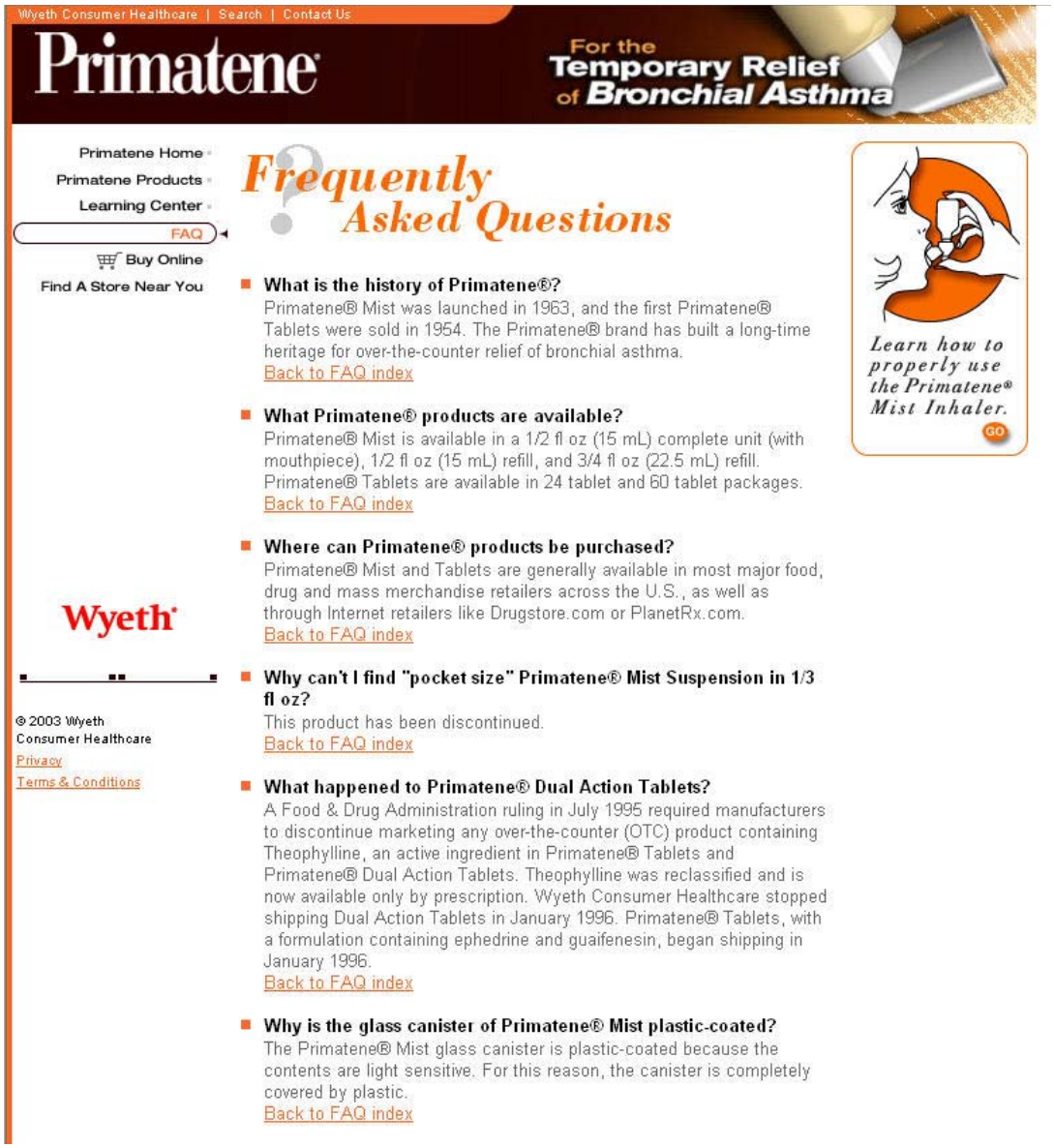
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Primatene
For the Temporary Relief of Bronchial Asthma
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Frequently Asked Questions
What is the history of Primatene®?
Primatene® Mist was launched in 1963, and the first Primatene® Tablets were sold in 1954. The Primatene® brand has built a long-time heritage for over-the-counter relief of bronchial asthma.
Back to FAQ index
What Primatene® products are available?
Primatene® Mist is available in a 1/2 fl oz (15 mL) complete unit (with mouthpiece), 1/2 fl oz (15 mL) refill, and 3/4 fl oz (22.5 mL) refill. Primatene® Tablets are available in 24 tablet and 60 tablet packages.
Back to FAQ index
Where can Primatene® products be purchased?
Primatene® Mist and Tablets are generally available in most major food, drug and mass merchandise retailers across the U.S., as well as through Internet retailers like Drugstore.com or PlanetRx.com.
Back to FAQ index
Why can't I find "pocket size" Primatene® Mist Suspension in 1/3 fl oz?
This product has been discontinued.
Back to FAQ index
What happened to Primatene® Dual Action Tablets?
A Food & Drug Administration ruling in July 1995 required manufacturers to discontinue marketing any over-the-counter (OTC) product containing Theophylline, an active ingredient in Primatene® Tablets and Primatene® Dual Action Tablets. Theophylline was reclassified and is now available only by prescription. Wyeth Consumer Healthcare stopped shipping Dual Action Tablets in January 1996. Primatene® Tablets, with a formulation containing ephedrine and guaifenesin, began shipping in January 1996.
Back to FAQ index
Why is the glass canister of Primatene® Mist plastic-coated?
The Primatene® Mist glass canister is plastic-coated because the contents are light sensitive. For this reason, the canister is completely covered by plastic.
Back to FAQ index
Learn how to properly use the Primatene® Mist Inhaler.
GO

- **Is the Primatene® Mist canister full?**
  The canisters are filled according to the weight of the liquid contents. The canisters also contain the appropriate amount of air needed for proper spraying action. When you hold the bottle up to a bright light, the visual fill level may vary from bottle to bottle, because each shipment of bottles can vary in thickness. The usable quantity of product in each unit is equal to or greater than the amount printed on the package label.
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- **How may puffs should I get from the vial?**
  The 15 mL vial should deliver 270 puffs and the 22.5 mL vial should deliver 405 puffs.
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- **Can I use a different mouthpiece with the vial?**
  No. Primatene® mouthpieces are specially designed for use with Primatene® Mist. The vial may not function correctly with another mouthpiece.
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- **How often should I clean my mouthpiece? What should be used?**
  The Primatene® mouthpiece should be washed after each use with soap and hot water, rinsed thoroughly, and dried with a clean, lint-free cloth.
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- **Can the mouthpiece be rinsed with alcohol?**
  No, this is not recommended.
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- **Is the mouthpiece dishwasher-safe?**
  No, as it will likely cause an improper fit and result in a vial that will not spray properly.
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- **May I buy a mouthpiece as a separate unit?**
  No, mouthpieces are only available in conjunction with the 1/2 fl oz size vial.
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- **Is the packaging recyclable?**
  The outer carton for both Primatene® Mist and Tablet products can be recycled. For the Complete Unit, the cellophane window must first be removed before recycling. Mouthpieces are reusable when washed regularly after each use. Glass canisters should be discarded when empty.
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- **Do any Primatene® products contain gelatin?**
  No. Primatene® products are gelatin-free.
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- **Do any Primatene® products contain lactose?**
  No. Primatene® products are lactose-free.
  Back to FAQ index

- **Do any Primatene® products contain lead?**
  No. Primatene® products are lead-free.
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- **Do any Primatene® products contain steroids?**
  No. Primatene® products do not contain steroids.
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- **Do any Primatene® products contain sulfites?**
  No. Primatene® products are free of sulfites.
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- **What is a bronchodilator?**
  Bronchodilators are a group of drugs that help widen the airways in the lungs for the treatment of asthma and other conditions which constrict airflow in the lungs. Bronchodilators widen the bronchioles, to increase the flow of air and improve breathing.
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- **What is an expectorant?**
  Expectorants are drugs that loosen mucus or phlegm in the lungs. Expectorants stimulate increased release of respiratory secretions. The increased release of secretions lowers the viscosity (thickness) of the bronchial secretions and permits easier removal from the respiratory tract.

  An expectorant may be used with productive and non-productive coughs, to increase the amount of sputum expectorated.
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- **What are the competitive products?**
  Primatene® is the leading national OTC asthma relief medication for both mist and tablets. Primary competitors include store brands and generic products.
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Primatene

For the Temporary Relief of Bronchial Asthma

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Wyeth

How do I properly use the Primatene® Mist Mouthpiece?

DIRECTIONS FOR USE OF MOUTHPIECE:

The Primatene® Mist mouthpiece, which is enclosed in the Primatene® Mist 15 mL size (not the refill size), should be used for inhalation only with Primatene® Mist.

1. Take plastic cap off mouthpiece. (For refills, use mouthpiece from previous purchase.)

2. Take plastic mouthpiece off bottle.

3. Place short end of mouthpiece on bottle.

4. Turn bottle upside down. Place thumb on bottom of mouthpiece over circular button and forefinger on top of vial. Empty the lungs as completely as possible by exhaling.

5. Place mouthpiece in mouth with lips closed around opening. Inhale deeply while squeezing mouthpiece and bottle together. Release immediately and remove unit from mouth, then complete taking the deep breath, drawing medication into your lungs, holding breath as long as comfortable.

6. Exhale slowly keeping lips nearly closed. This helps distribute the medication in the lungs.

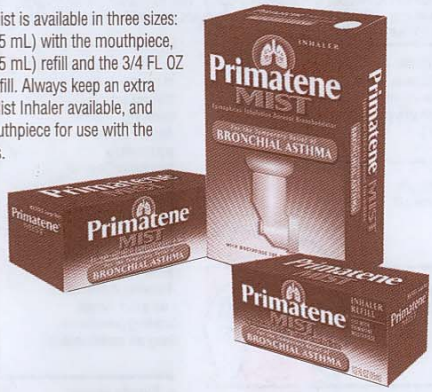
7. For storage, place long end of mouthpiece back on bottle and cover with plastic cap.

Care of Mouthpiece: The Primatene® Mist mouthpiece should be washed after each use with hot, soapy water, rinsed thoroughly, and dried with a clean, lint-free cloth.

If the unit becomes clogged and fails to spray, please write and send the clogged unit to: Wyeth Consumer Healthcare, P.O. Box 26609, Richmond, VA 23261-6609.

Package Insert - (prior to July 2005 Proposed Rule)

Primatene Mist is available in three sizes: 1/2 FL OZ (15 mL) with the mouthpiece, 1/2 FL OZ (15 mL) refill and the 3/4 FL OZ (22.5 mL) refill. Always keep an extra Primatene Mist Inhaler available, and save the mouthpiece for use with the Inhaler refills.



Epinephrine Inhalation Aerosol Bronchodilator
For the Temporary Relief of BRONCHIAL ASTHMA

Epinephrine Inhalation Aerosol Bronchodilator
For the Temporary Relief of BRONCHIAL ASTHMA

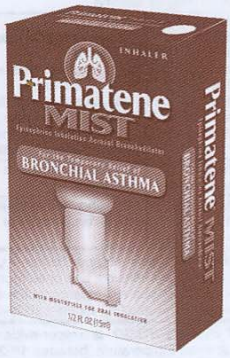
BENEFITS OF PRIMATENE MIST
When used according to directions, Primatene Mist provides an easy and effective way to obtain temporary relief of bronchial asthma. Primatene Mist has been used safely by millions. Primatene Mist contains epinephrine, which is a dependable inhalation aerosol bronchodilator. It is packaged in a plastic-coated safety-glass bottle, fitted with a specially designed valve, for use with the Primatene Mist mouthpiece only. The special valve is designed to deliver the same amount of medication with each spray. Primatene Mist can be used at any time of the day or night.

ASTHMA SUFFERERS AND SULFITES Sulfites, a popular food and drug preservative, can cause severe bronchospasms in sensitive individuals, especially asthmatics. If you suspect that you are sulfite sensitive, check with your doctor. **Primatene Mist contains no sulfites.**

Primatene Tablets are available in two sizes, 24 count and 60 count.

Primatene® MIST

Primatene® MIST



Whitehall-Robins Healthcare, Madison, NJ 07940 Made in USA 2910-20/15J

Active ingredient (in each inhalation) — ***Purpose***
Epinephrine 0.22 mg ..... Bronchodilator

Uses
- temporarily relieves shortness of breath, tightness of chest, and wheezing due to bronchial asthma
- eases breathing for asthma patients by reducing spasms of bronchial muscles

Warnings
For inhalation only

Do not use
- unless a doctor has said you have asthma
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have
- heart disease
- thyroid disease
- diabetes
- high blood pressure
- ever been hospitalized for asthma
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking any prescription drug for asthma

When using this product
- overuse may cause nervousness, rapid heart beat, and heart problems
- **do not continue to use, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse**
- do not puncture or throw into incinerator. Contents under pressure.
- do not use or store near open flame or heat above 120°F (49°C). May cause bursting.

Contains CFC 12, 114, substances which harm public health and environment by destroying ozone in the upper atmosphere

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- **do not use more often or at higher doses unless directed by a doctor**
- supervise children using this product
- adults and children 4 years and over: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours.
- children under 4 years of age: ask a doctor

Other information
- store at room temperature, between 20-25°C (68 -77°F)
- contains no sulfites
- see insert for mouthpiece use and care instructions

Inactive ingredients ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water

DIRECTIONS FOR USE OF MOUTHPIECE The Primatene Mist mouthpiece, which is enclosed in the Primatene Mist 15 mL size (not the refill size), should be used for inhalation only with Primatene Mist.

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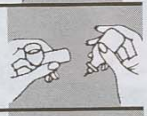

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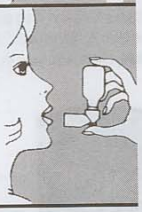

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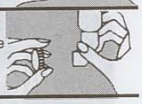

CARE OF THE MOUTHPIECE The Primatene Mist mouthpiece should be washed after each use with hot, soapy water, rinsed thoroughly, and dried with a clean, lint-free cloth.

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Questions or comments? Call **1-8 PRIMATENE** or **1-877-462-8363** weekdays 9 AM-5 PM EST
www.Primatene.com