Federal Aviation
Administration

DOT/FAA/AM-07/12
Office of Aerospace Medicine
Washington, DC 20591

First-Generation H_1 Antihistamines Found in Pilot Fatalities of Civil Aviation Accidents, 1990–2005

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May 2007

Final Report

NOTICE

Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT/FAA/AM-07/12		

4. Title and Subtitle	5. Report Date
First-Generation H_1 Antihistamines Found in Pilot Fatalities of Civil Aviation Accidents, 1990–2005	May 2007
	6. Performing Organization Code

7. Author(s)	8. Performing Organization Report No.
Sen A,[1] Akin A,[1] Craft KJ,[2] Canfield DV,[2] Chaturvedi AK[2]	

9. Performing Organization Name and Address		10. Work Unit No. (TRAIS)
[1]Department of Aerospace Medicine Gülhane Military Medical Academy Eskisehir 26020, Turkey	[2]FAA Civil Aerospace Medical Institute P.O. Box 25082 Oklahoma City, OK 73125	11. Contract or Grant No.

12. Sponsoring Agency name and Address	13. Type of Report and Period Covered
Office of Aerospace Medicine Federal Aviation Administration 800 Independence Ave., S.W. Washington, DC 20591	14. Sponsoring Agency Code

15. Supplemental Notes

This work was accomplished under the approved task AM-B-07-TOX-202.

16. Abstract

First-generation H_1-receptor antagonists are popularly used for alleviating allergy and cold symptoms, but these antihistaminics cause drowsiness and sedation. Such side effects could impair performance and, thus, could be the cause or a factor in accidents. Therefore, the prevalence of these antagonists was evaluated in aviation accident pilot fatalities. During civil aircraft accident investigations, postmortem samples from pilots involved in fatal aviation accidents are submitted to the Civil Aerospace Medical Institute (CAMI) for toxicological analyses. These analytical findings are stored in a database. This CAMI Toxicology Database was examined for the presence of the first-generation antihistamines in pilot fatalities of civil aircraft accidents that occurred during a 16-year (1990–2005) period. Of 5383 fatal aviation accidents from which CAMI received specimens, there were 338 accidents wherein pilot fatalities (cases) were found to contain the antihistaminics brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine, and triprolidine. Of the 338 accidents, 304 were general aviation accidents; 175 of the 338 pilots held private pilot airman certificates. Antihistamines were detected alone in 103 fatalities (1 antihistamine in 94 fatalities and 2 antihistamines in 9), while other drug(s) and/or ethanol were also present in an additional 235 fatalities. Thirty-five of the 338 fatalities had more than 1 antihistamine. The antihistamines were found in approximately 4 and 11% of the fatalities/accidents in 1990 and in 2004, respectively. Although blood was not available for the analyses in all 338 cases, the blood concentrations ($ng \cdot mL^{-1}$) were 5–200 (n = 8) for brompheniramine; 4–6114 (n = 67) for chlorpheniramine; 9–3800 (n = 125) for diphenhydramine; 10–1309 (n = 33) for doxylamine; and 4 (n = 1) for phenyltoloxamine. The use of antihistamine(s), with/without other drug(s) and/or ethanol, was determined by the National Transportation Safety Board to be the cause in 13 and a factor in 50 of the 338 accidents. The majority of the accidents were of the general aviation category. There was an overall increasing trend in the use of antihistamines by aviators during the 16-year span. Blood levels of the antihistaminics were in the sub-therapeutic to toxic range. Findings from this study will be useful in investigating future accidents involving antihistamines.

17. Key Words	18. Distribution Statement
Forensic Sciences, Toxicology, Pilot Fatalities, First-Generation Antihistamines, Antihistaminics, Aviation Accident Investigation	Document is available to the public through the Defense Technical Information Center, Ft. Belvior, VA 22060; and the National Technical Information Service, Springfield, VA 22161

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	17	

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ACKNOWLEDGMENTS

The Government of Turkey is acknowledged for allowing the participation of Dr. Ahmet Akin and Dr. Ahmet Sen in the Federal Aviation Administration (FAA) International Exchange Visitor Program at the FAA Civil Aerospace Medical Institute, Oklahoma City, Oklahoma.

The authors are grateful to Dr. Selim Kilic, Department of Epidemiology, Gülhane Military Medical Academy, Ankara, Turkey, for performing statistical analyses.

First-Generation H_1 Antihistamines Found in Pilot Fatalities of Civil Aviation Accidents, 1990–2005

INTRODUCTION

Although many drugs are pharmacologically classified under the category of first-generation H_1-receptor antagonists (FGH_1As), all of them are not used for alleviating allergy and common cold symptoms (24). The most commonly used FGH_1As for treating these medical conditions are azatadine, bromazine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, and triprolidine (27). These 13 antihistaminics are primarily marketed as nonprescription medications; however, depending upon their pharmaceutical formulations and preparations, they are also marketed as prescription drugs. These FGH_1As are available in various tablet, capsule, caplet, elixir, ointment, and/or injection forms with or without analgesics, decongestants, antitussives, expectorants, and/or other H_1 antagonists (19,20).

FGH_1As depress the Central Nervous System (CNS), causing diminished alertness, slowed reaction times, dizziness, and sedation (24). Therefore, patients are cautioned against operating a vehicle or machinery while using the medications (20,27). FGH_1AI-induced sedation does not only comprise subjective symptoms, like sleepiness, lethargy, or subtle confusion, but also reflects the objective impairment of superior cognitive functions (15). The first-generation antihistamines have been reported to be associated with significant sleepiness and impaired performance on flight tasks, resulting in slowed reaction times, memory difficulties, and impaired vigilance (6,12,16–18,22,28,29). Consequently, this group of medications is known to impair superior cognitive functions and, thus, these drugs have the potential for impairing in-flight performance. Because of the adverse effects, the first-generation antihistamines are not approved for use by civilian aviators (10,13,23).

The presence of pheniramine in aviation accident fatalities has been documented as early as the 1960s (5). Brompheniramine, diphenhydramine, and pheniramine have been reported to be present in the ground transportation fatalities in 1978–1979 (9) and chlorpheniramine in civil aviation accident pilot fatalities in 1991–1996 (25). However, detailed information about the prevalence and causal effects of FGH_1As in fatal civil aviation accidents is not well documented. Since the field of aviation forensic toxicology is basically a human performance-related postmortem forensic toxicology undertaking, findings on the prevalence of FGH_1As in civil aviation accident pilot fatalities, along with their concentrations in the associated postmortem blood samples, would be useful in the investigations of FGH_1AI-involved aviation accidents. Therefore, relevant databases were searched to retrieve the applicable necessary information. The findings from the database searches are presented herein.

METHODS

Postmortem Samples

During the investigation of civil aviation accidents occurring within U.S. jurisdiction, autopsied biological samples—blood, urine, vitreous fluid, spinal fluid, brain, lung, heart, liver, kidney, and/or other sample types—collected from pilot fatalities are submitted to the Civil Aerospace Medical Institute (CAMI) for toxicological evaluation (3). The submission of specimens is coordinated through the Federal Aviation Administration's (FAA's) Office of Accident Investigation by the National Transportation Safety Board (NTSB), which is responsible for investigating all U.S. civilian aircraft accidents. The collected samples are shipped in the FAA's TOX-BOX evidence containers (8). The aviation accidents include accidents associated with registered, as well as unregistered, aircraft.

Toxicology

The submitted biological samples are routinely analyzed for the presence of carbon monoxide and hydrogen cyanide, ethanol and other volatiles, and drugs (7,8). The drugs include a wide range of prescription, nonprescription, and illicit drugs. The analyses of all of these foreign substances (analytes) are conducted according to established standard laboratory procedures, including initial and confirmatory/quantitative analyses (8). Such analyses are dependent upon the nature of analytes, the sensitivity and specificity of analytical methods used, and the availability of specimen types and their amounts. FGH_1As in the biological samples were screened (initial analysis) by high-performance liquid chromatography and by gas chromatography/mass spectrometry (GC/MS) and were confirmed/quantitated by GC/MS. The quantitative analyses of the antihistamines were generally conducted in blood specimens and the confirmatory analyses in other sample types. In those cases wherein blood samples were

not available for the analysis, the FGH_1AIs were analyzed in other available specimen types.

Databases

The CAMI's Toxicology Database (Oklahoma City, OK), maintained since 1990, was descriptively examined for the presence of the 13 first-generation antihistamines azatadine, bromazine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, and triprolidine (with or without any other drug(s) and/or ethanol) in pilot fatalities of civil aviation accidents that occurred during a 16-year (1990–2005) period. The Toxicology Database was also searched to ascertain the number of 1990–2005 aviation accidents and associated pilot fatalities from which CAMI received postmortem biological samples. The percentage of the FGH_1AI-involved fatal accidents in the total pilot fatality-involved accidents for each year was determined for the period of 1990 to 2005. Such percentages reflected the equivalent values of the antihistamine-associated pilot fatalities in the total pilot fatalities from which samples were received for those years.

Since each fatality is given a specific CAMI case number, the fatality is also referred to as a case. Therefore, "fatality" and "case" are used interchangeably in the present study. Fatalities included herein consisted of only pilots; copilots were not included.

Information on the types of airman medical and flying certificates held by those FGH_1AI-involved pilots was retrieved from the CAMI Toxicology Database and from the NTSB's Aviation Accident Database (Washington, DC). However, it should be noted that not all of the pilots involved in the accidents had the appropriate airman flying and/or medical certificates required to legally pilot an aircraft. The number of fatal aviation accidents reported by the NTSB for the 1990–2005 period was obtained from the FAA's National Aviation Safety Data Analysis Center (NASDAC) Database (Washington, DC). The information for the FGH_1AI-related accidents, including the probable cause and contributing factors of those accidents, as determined and reported by the NTSB, was retrieved from the NTSB Aviation Accident Database. The cause and factors-related information included in the study is based on the findings reported in the NTSB Database through September 2006. Since the NASDAC Database includes information primarily associated with the accidents of registered aircraft, information on the accidents of unregistered aircraft may not necessarily be included in this database. However, the CAMI Toxicology Database might also include information for the unregistered aircraft accidents.

Statistics

The proportion (percentage) of the FGH_1AI-involved fatal accidents/pilot fatalities in the total pilot fatality-involved accidents/pilot fatalities per year was calculated for each year. The difference of percentages in years was analyzed by Chi-square test using SPSS® for Windows® 10.0 (SPSS Inc., Chicago, IL). The proportional values were plotted against the corresponding years, and a trend line was drawn by using Microsoft® Office Excel 2003 (Redmond, WA).

RESULTS

Accidents and Pilot Fatalities

As reported in the NASDAC Database, the number of all the U.S. fatal civil aviation accidents for the 1990–2005 period was 7194 (Table I). Out of these accidents, 5891 were of general aviation, 376 air taxi and commuter, 51 air carrier, 199 agricultural, and 6 ultralight vehicle categories. The remaining 671 accidents were of other flight categories. The accidents under the air taxi and commuter category included both scheduled and non-scheduled flights.

During 1990–2005, CAMI received and toxicologically evaluated postmortem samples from 5281 pilot fatalities associated with 5383 accidents (Table I). Of the 5383 accidents, 4734 (4655 pilots) were of general aviation, 271 (265 pilots) air taxi and commuter, 27 (20 pilots) air carrier, and 157 (157 pilots) agricultural categories; 194 accidents (184 pilots) were associated with other categories, including ultralight vehicle and public use categories. Therefore, the 5281 pilot fatalities correspond to the equivalent number of aviation accidents wherein pilot fatalities occurred and their postmortem samples were toxicologically evaluated.

Antihistamine-Involved Accidents and Pilot Fatalities

Flight categories: Of the 5383 accidents from which postmortem samples were submitted to CAMI, FGH_1AIs were found in 338 pilot fatalities, translating into the equivalent number of aviation accidents (Table I). Of the 338 accidents, 304 were general aviation, 15 air taxi and commuter, 1 air carrier, 8 agricultural, 2 rotorcraft, and 4 ultralight vehicle flights. The remaining 4 accidents occurred during public use and other flights.

Airman flying and medical certificate categories: Out of the 338 FGH_1AI-involved pilots, 175 held private, 88 commercial, 48 airline transport, 20 student, 1 foreign, and 1 recreational airman flying certificates (Fig. 1). The remaining 5 pilots were non-certificated. Of the 175 private pilot certificate holders, 172 were involved in general aviation accidents, while 3 in ultralight vehicle accidents.

Table I. Operation Type-Based Categorization of Fatal Civil Aviation Accidents (1990–2005) Reported in the FAA NASDAC Database and in the CAMI Toxicology Database

Operation Categories*	Accidents in FAA NASDAC Database†	CAMI Toxicology Database‡		
		Aviation Accidents	Pilot Fatalities§	FGH_1AI-Related Pilot Fatalities§
General aviation (14 CFR Part 91)	5891	4734	4655	304
Air taxi and commuter (14 CFR Part 135)	376	271	265	15
Air carrier (14 CFR Part 121)	51	27	20	1
Agricultural (14 CFR Part 137)	199	157	157	8
Rotorcraft (14 CFR Part 133)	43	30	29	2
Ultralight vehicle (14 CFR Part 103)	6	47	47	4
Public use	63	69	66	2
Other categories	565	48	42	2
Total	7194	5383	5281	338

*Code of Federal Regulations (CFR), Title 14 Parts (11).

†May not include fatal accidents of unregistered aircraft, such as ultralight vehicles.

‡Includes fatal accidents of registered and unregistered aircraft from which postmortem biological samples were submitted for toxicological evaluation.

§Translates into the equivalent number of aviation accidents.

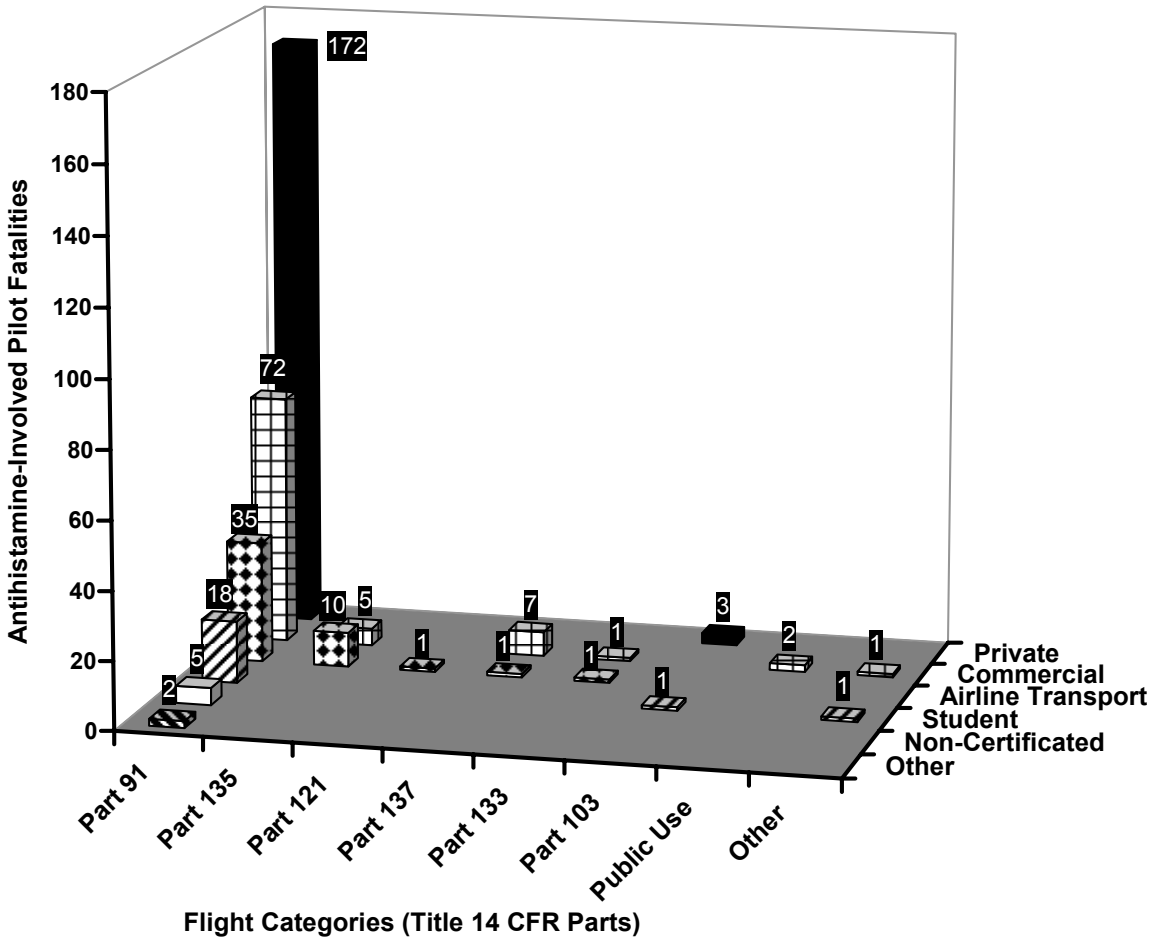

Figure 1. Antihistamine-associated pilot fatalities with respect to airman flying certificates and flight categories (Title 14 CFR Parts) of the aircraft involved in the fatal accidents (1990–2005). The description of flight categories under Title 14 CFR Parts are given in Table I.

In the 88 commercial pilot certificate holders, 72 were involved in general aviation, 5 in air taxi and commuter, 7 in agricultural, 1 in rotorcraft, 2 in public use, and 1 in other flight accidents. Under the category of the 48 airline transport pilot certificate holders, 35 were involved in general aviation, 10 in air taxi and commuter, 1 in air carrier, 1 in agricultural, and 1 in rotorcraft accidents. There were 20 student pilot certificate holders. Of these student pilots, 18 were involved in general aviation, 1 in an ultralight vehicle, and 1 in other flight accidents. The remaining pilots—5 non-certificated and 2 other pilots—were involved in general aviation accidents.

Thirty-five of the 338 pilots held First-Class, 107 Second-Class, and 182 Third-Class airman medical certificates (Fig. 2). The remaining 14 pilots did not hold valid medical certificates. Of the 35 First-Class medical certificate holders, 27 were involved in general aviation accidents, followed by 7 in air taxi and commuter, and 1 in air carrier accidents. Out of the 107 pilots with Second-Class medical certificates, 85 were involved in general aviation, 8 in air taxi and commuter, 8 in agricultural, 2 in rotorcraft, 1 in ultralight vehicle, 2 in public use, and 1 in other category accidents. Three of the 182 Third-Class medical certificate-holding pilots were involved in ultralight vehicle accidents, while the remaining in general aviation accidents. Thirteen of the 14 non-certificated pilots were involved in general aviation accidents and 1 in other category accident.

Antihistamine-Related Toxicological Findings

The search of the Toxicology Database revealed the presence of 8 FGH_1AIs—brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, promethazine, and triprolidine—in the pilot fatalities during the 16-year period (Fig. 3). Fatalities with chlorpheniramine, diphenhydramine, and doxylamine were noted every year during 1990–2005. The highest number of 191 fatalities was associated with

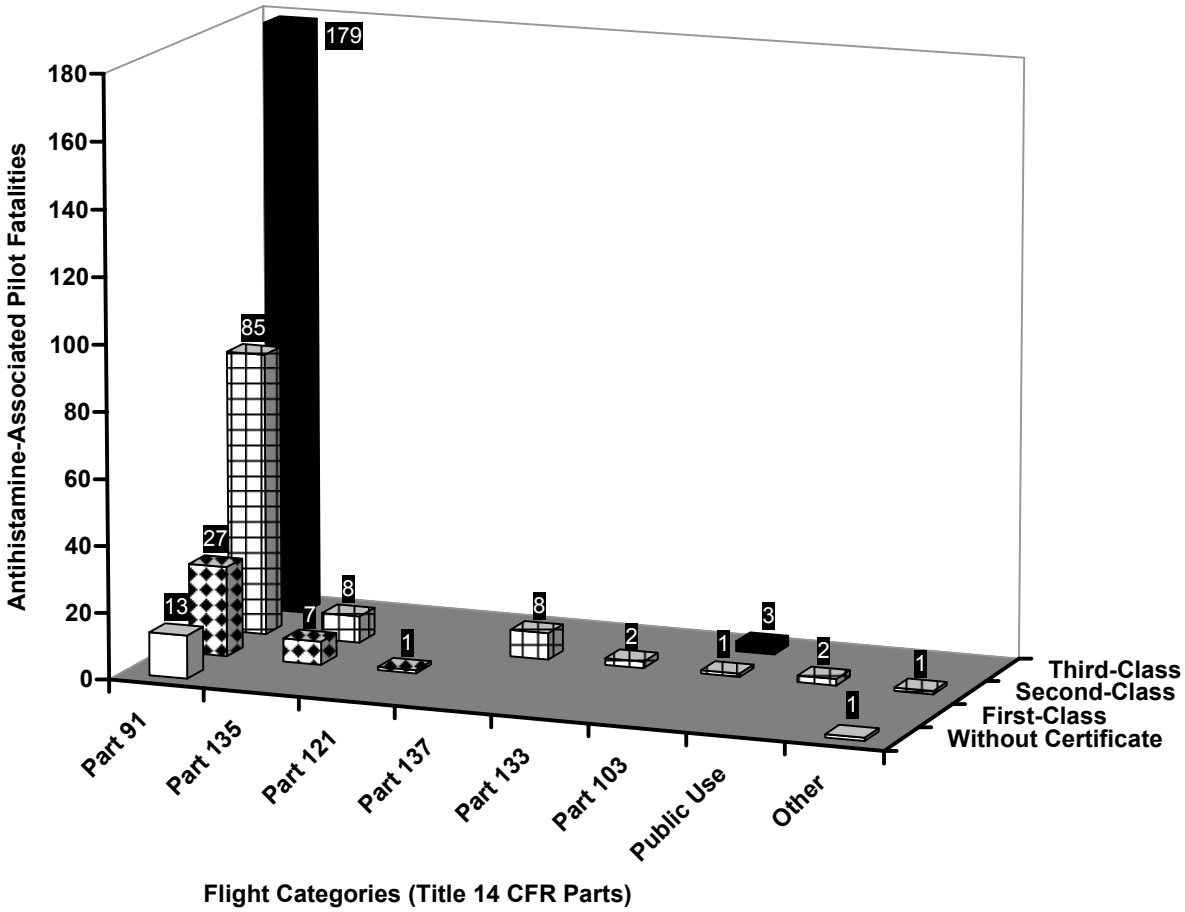

Figure 2. Antihistamine-involved pilot fatalities with respect to airman medical certificates and flight categories (Title 14 CFR Parts) of the aircraft associated with the fatal accidents, 1990–2005. Flight categories under Title 14 CFR Parts are described in Table I.

diphenhydramine, followed by 112 with chlorpheniramine, and 50 with doxylamine (Table II).

As given in Table II, 94 of the 338 pilots had only 1 antihistamine, while 244 had other drug(s) and/or ethanol as well. Two antihistaminics—one being diphenhydramine and the other being brompheniramine, chlorpheniramine, doxylamine, or promethazine—were detected in 9 pilots without any other drug or ethanol. However, any 2 of the antihistaminics—brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, phenyltoloxamine, and promethazine—were found in 25 pilots with other drug(s) and/or ethanol. In 1 fatality (case), 3 antihistaminics—chlorpheniramine, diphenhydramine, and doxylamine—were detected along with other drugs. There were 209 fatalities in which only 1 antihistamine, along with other drugs and/or ethanol, was present. Excluding the 8 FGH_1AIs (Table II), other drugs found in the fatalities entailed amphetamines and other sympathomimetics, analgesics (narcotic and non-narcotic), antidepressants, atropine, barbiturates, benzodiazepines, cardiovascular agents, cocaine, lidocaine, and tetrahydrocannabinol carboxylic acid. Carboxyhemoglobin (≥10%) and/or blood cyanide (≥ 0.25 μg·mL–1) were determined to be elevated in 14 pilot fatalities. Fire was reported in 12 of these 14 accidents.

The percentages of the antihistamine-involved pilot fatalities with respect to the total number of pilot fatalities (cases), during the 16-year period, from which samples were received at CAMI, clearly suggested a steady increase in the number of fatalities with these medications (Fig. 4). For example, the antihistamine-associated fatalities/aviation accidents were approximately 4 and 11% in 1990 and 2004, respectively. The difference in the proportions of the FGH_1AI-involved fatal accidents/pilot fatalities in the total fatal accidents/pilot fatalities per year was statistically significant (Chi-square = 57.22; df = 15; $p < 0.001$).

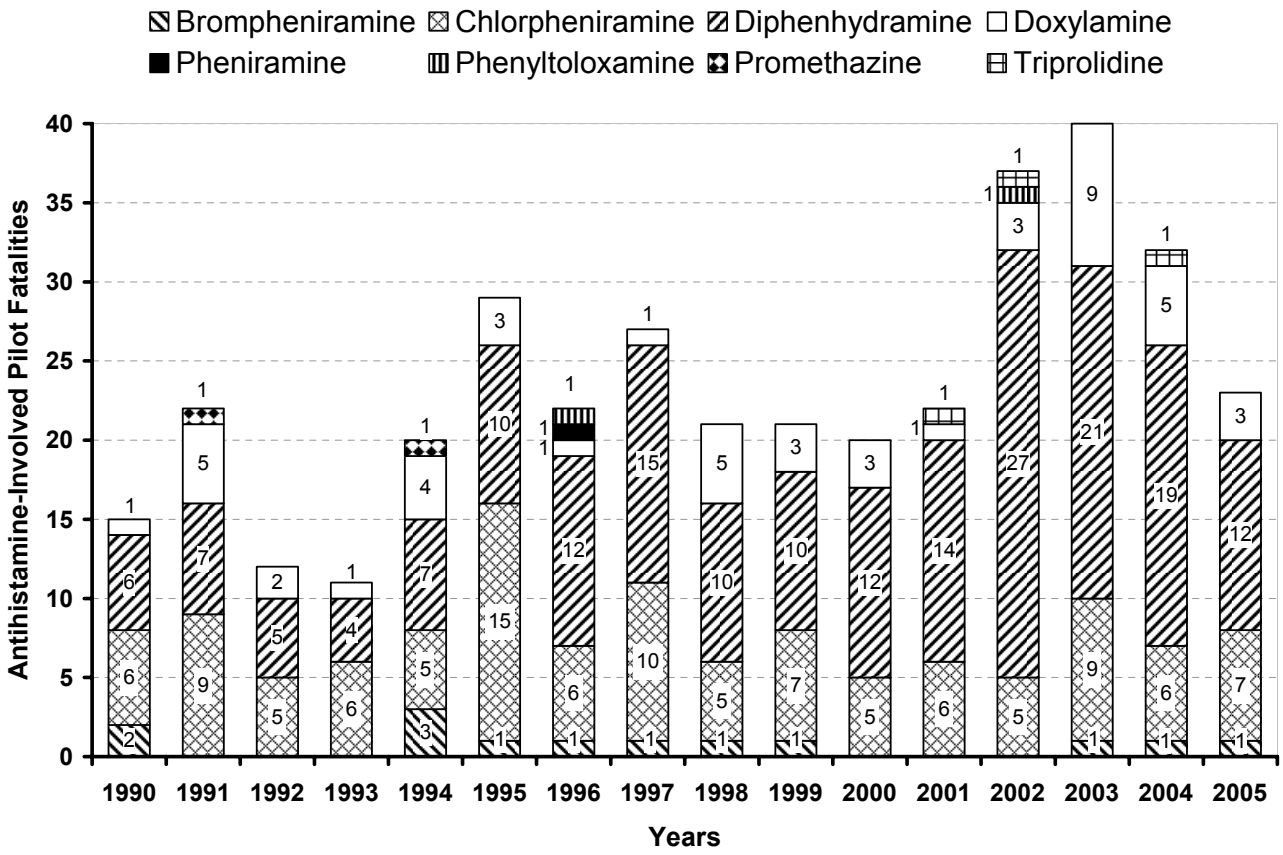

Figure 3. First-generation antihistamine-associated pilot fatalities (cases) of civil aviation accidents, 1990–2005.

Table II. First-Generation Antihistamines Found in the 338 Pilot Fatalities (Civil Aviation Accidents, 1990–2005)

Antihistamines	Pilot Fatalities	
	With Only 1 Antihistamine	Also With Other Substance(s)*
Brompheniramine	2	11
Chlorpheniramine	26	86
Diphenhydramine	60	131
Doxylamine	6	44
Pheniramine	0	1
Phenyltoloxamine	0	2
Promethazine	0	2
Triprolidine	0	3
Total	94	280†

*Includes other antihistamines, drugs, and/or ethanol.

†34 fatalities (cases) had 2 antihistaminics; 1 had 3 antihistaminics.

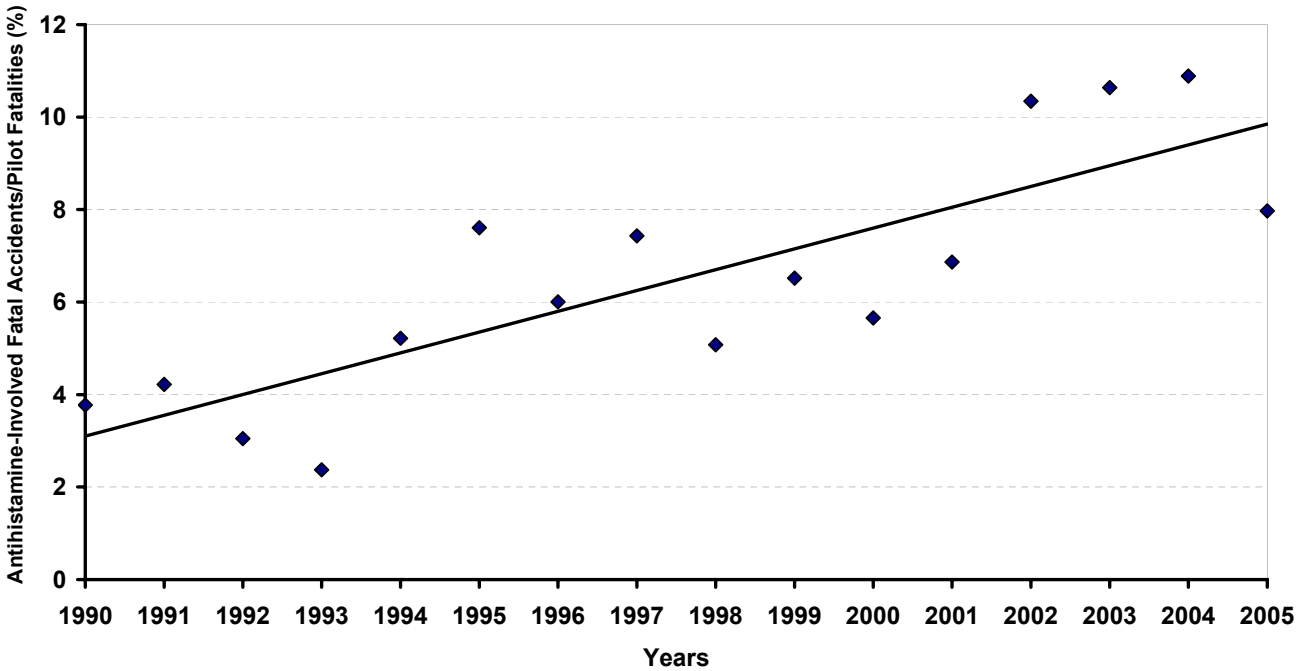

Figure 4. The percentage of the antihistamine-involved fatal accidents/pilot fatalities in the total pilot fatality-involved accidents/pilot fatalities per year from which samples were received at CAMI for toxicological evaluation. There is a statistically significant difference in percentages with respect to years (Chi-square = 57.22; df = 15; $p < 0.001$).

Diphenhydramine: Of the 191 diphenhydramine-associated pilots (cases), only diphenhydramine was detected in 60 cases (Table II). Blood was not available in 22 of the 60 cases. The blood concentration range of diphenhydramine was 14–3800 ng·mL–1 (n = 38; Table III). In the remaining 131 cases, other drugs and/or ethanol were also detected. Blood was not available in 44 of the 131 cases. The blood diphenhydramine concentration in those cases wherein other drugs and/or ethanol were present ranged from 9 to 806 ng·mL–1 (n = 87). Ethanol was found in 23 cases.

Chlorpheniramine: Out of the 112 pilots (cases) wherein chlorpheniramine was detected, only chlorpheniramine was found in 26 cases (Table II). Blood was not available in 12 of these cases. The chlorpheniramine concentration in blood was 7–151 ng·mL–1 (n = 14; Table III). In the remaining 86 cases, other drugs and/or ethanol were also found. Blood was not available in 33 of the 86 cases. The blood chlorpheniramine concentration in those cases wherein other drugs and/or ethanol were present ranged from 4 to 6114 ng·mL–1 (n = 53). Ethanol was found in 18 cases.

Doxylamine: This drug was found in 50 pilot fatalities (cases). In 6 of these cases, only doxylamine was detected (Table II). Blood was not available in 3 of the 6 cases. The blood concentration range of doxylamine was 64–300 ng·mL–1 (n = 3; Table III). In the remaining 44 cases, other drugs and/or ethanol were also present. Blood was not available in 14 of the 44 cases. The doxylamine concentration in blood of those cases wherein other drugs and/or ethanol were present ranged from 10 to 1309 ng·mL–1 (n = 30). Ethanol was found in 6 cases.

Brompheniramine: This antihistamine was found in 13 pilots (cases). In 2 of the cases, only brompheniramine was detected (Table II). Blood was available in only 1 case, and the blood concentration of brompheniramine was determined to be 200 ng·mL–1 (Table III). In the remaining 11 cases, other drugs and/or ethanol were also found. Blood was not available in 4 of the 11 cases. The blood brompheniramine concentration in those cases wherein other drugs and/or ethanol were present ranged from 5 to 100 ng·mL–1 (n = 7). Ethanol was found in 1 case.

Triprolidine: Only 3 pilot fatalities (cases) were associated with this drug (Table II). Other drugs—butalbital, diazepam, ephedrine, paroxetine, phenylpropanolamine, pseudoephedrine, quinine, and/or tetrahydrocannabinol carboxylic acid—were also present in the fatalities. Blood was not available for the analysis in these cases.

Phenyltoloxamine: There were only 2 pilot fatalities (cases) associated with this antihistamine (Table II). Chlorpheniramine, ephedrine, phenylpropanolamine, and pseudoephedrine were also detected in one case and pheniramine and phenylpropanolamine in the other. Blood was available in 1 case; the concentration of the drug was 4 ng·mL–1 (Table III).

Table III. Blood Antihistamine Concentrations Found in Civil Aviation Accident Pilot Fatalities

Antihistamines	Blood Concentration ($ng \cdot mL^{-1}$)	
	Without Other Substance	With Other Substance(s)*
Brompheniramine	200 (n = 1)	5 – 100 (n = 7)
Chlorpheniramine	7 – 151 (n = 14)	4 – 6114 (n = 53)
Diphenhydramine	14 – 3800 (n = 38)	9 – 806 (n = 87)
Doxylamine	64 – 300 (n = 3)	10 – 1309 (n = 30)
Pheniramine	–	–
Phenyltoloxamine	–	4 (n = 1)
Promethazine	–	–
Triprolidine	–	–

*Includes other antihistamines, drugs, and/or ethanol.

Promethazine: As given in Table II, this drug was found in 2 pilot fatalities (cases). Ethanol was detected in both cases and pseudoephedrine in 1. Blood was not available in either case.

Pheniramine: This antihistamine was found in just 1 fatality (Table II). Phenylpropanolamine and phenyltoloxamine were also detected. Blood was not available for analysis.

Antihistamine Use as Aviation Accident Cause/Factor

Based on the information available in the NTSB Database through September 2006, the use of the antihistamine(s) by pilots was determined to be the probable cause or a contributing factor in 63 of the 338 accidents (Fig. 5). The reports of 330 accidents have been finalized, but 8 have not yet been completed. There were 13 accidents in which the use of antihistamine(s) was determined to be the cause of the accidents. In 1 pilot fatality, only 1 antihistamine was found. However, other drugs and/or ethanol were also present in 12 fatalities. Of these, 5 had 2 antihistamines and 1 had 3 antihistamines. In 50 accidents, the use of antihistamine(s) was determined to be a contributing factor. This group of accidents entailed 7 fatalities in which only 1 antihistamine was found. Other drugs and/or ethanol (other substances) were also present in the remaining 43 fatalities. Five of the 43 cases had 2 antihistaminics.

Diphenhydramine: Of the 191 diphenhydramine-involved accidents, the use of this medication was determined by the NTSB to be the cause in 8 accidents, of which 1 pilot had only diphenhydramine, while 7 also had other drug(s). Additionally, the use of this antihistamine was determined to be a contributing factor in 26 accidents, of which 3 pilots had only diphenhydramine, while 23 also had other drug(s) and/or ethanol (Fig. 5). Of the 34 (8 + 26) accidents, 31 were in general aviation, 1 agricultural, 1 ultralight vehicle, and 1 public use categories. The cause/factor of 1 accident was undetermined, and the final reports of 3 accidents were unavailable in the NTSB database. The use of this antihistamine was not reported by the NTSB to be the cause or a factor in 153 of the 191 accidents.

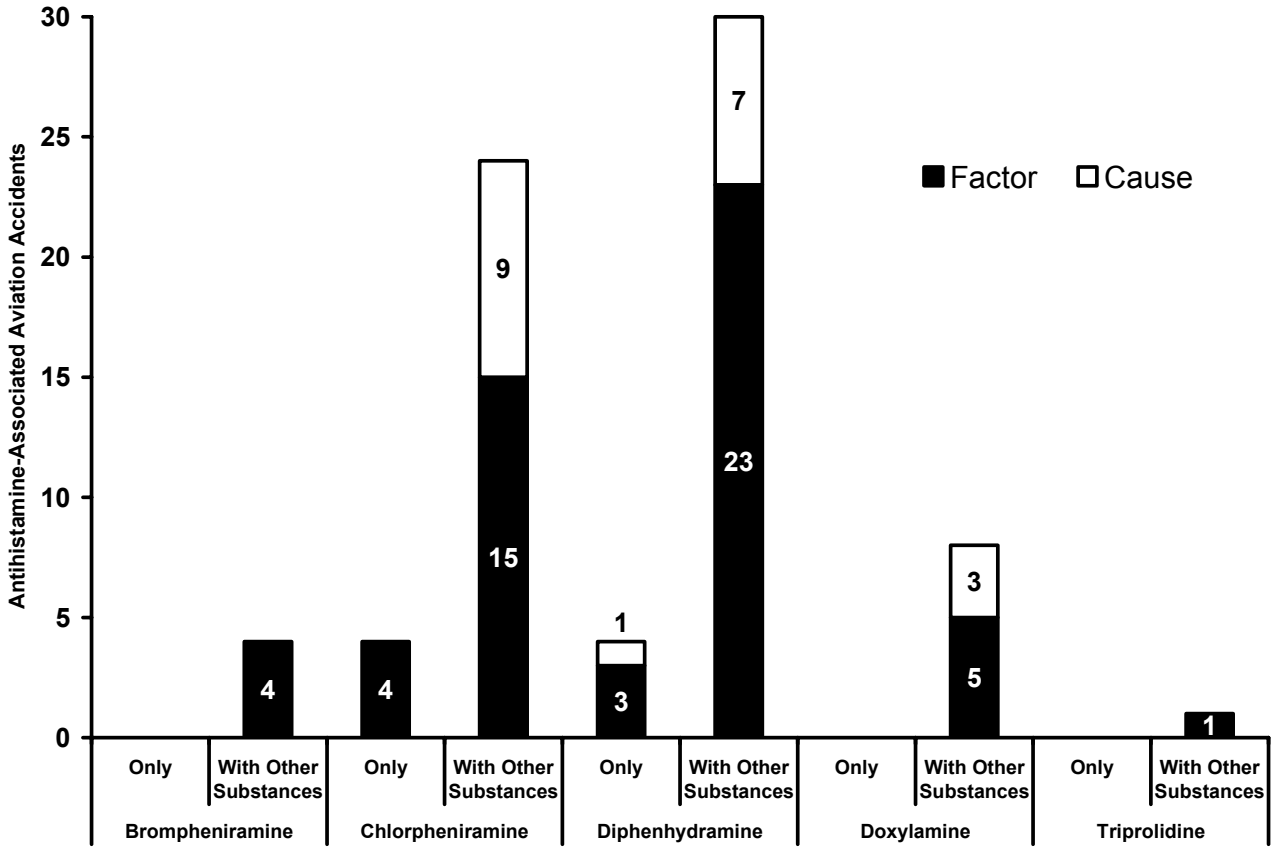

Figure 5. Fatal aviation accidents wherein the use of antihistamine(s) was determined by the NTSB to be the probable cause or a contributing factor. These accidents included the presence of first-generation antihistaminic(s), with or without other drugs and/or ethanol (other substances), in the associated pilot fatalities. Under the "Cause" group, 5 fatalities had 2 antihistamines and 1 fatality had 3; 5 fatalities had 2 antihistamines under the "Factor" group.

Chlorpheniramine: Of the 112 chlorpheniramine-associated accidents, the use of chlorpheniramine was established by the NTSB to be the cause of 9 accidents. Other drugs and/or ethanol were also found in the 9 accident pilot fatalities. The use of chlorpheniramine was reported to be a contributing factor in 19 accidents, of which 4 pilots had only chlorpheniramine, while the remaining also had other drug(s) and/or ethanol (Fig. 5). Of the 28 (9 + 19) accidents, 26 were in general aviation, 1 air taxi and commuter, and 1 agricultural categories. The cause/factor of 1 accident was not determined, and the final reports of 5 accidents were not available in the NTSB database. Chlorpheniramine use was not reported by the NTSB to be the cause or a factor in 78 of the 112 accidents.

Doxylamine: Of the 50 doxylamine-involved cases, the use of this antihistamine was found by the NTSB to be the cause in 3 accidents and a contributing factor in 5. With all of the 8 (5 + 3) fatalities, other drug(s) and/or ethanol were also found (Fig. 5). Of these accidents, 7 were of general aviation and 1 air taxi and commuter categories. The cause/factor of 1 accident was undetermined. The use of doxylamine was not reported by the NTSB to be the cause or a factor in 41 of the 50 accidents.

Brompheniramine: The use of this drug was established by the NTSB to be a contributing factor in 4 of the 13 brompheniramine-involved accidents. Other drugs were also found in the 4 aviation accident fatalities (Fig. 5). These 4 accidents were of general aviation category. The brompheniramine use was not reported by the NTSB to be the cause or a factor in 9 of the 13 accidents.

Triprolidine: The NTSB determined the use of medications to be a contributing factor in 1 of the total 3 accidents related to this antihistamine. The use of this drug was not found to be the cause or a factor in the remaining 2 accidents.

Phenyltoloxamine: The drug use was not established to be the cause or a factor by the NTSB for the total 2 accidents associated with this antihistamine.

Promethazine: In the total 2 accident pilot fatalities wherein this antihistamine was found, the use of the drug was not established to be the cause or a factor by the NTSB.

Pheniramine: There was only 1 accident involving pheniramine. The use of this FGH_1AI was not determined by the NTSB to be the cause or a factor in the accident.

DISCUSSION

The physical and mental wellbeing of airmen plays a crucial role in the safe and successful operation of an aircraft, and this activity requires the integration of higher cognitive skills. Pilots are not only cautioned for the medical conditions that might interfere with flight safety, but also against the potential impact of some drugs, even when pilots feel better by taking them (13,23). Among these drugs, the most important are the ones that alter CNS functions. Although FGH_1AIs are not CNS-specific drugs, as such, they have major side effects on the CNS (24,27). Because of this very reason, the package labeling of these medications contains precautionary statements, warning users against activities involving motor skills, such as operating a vehicle or machinery. However, patients—including aviators—do not appear to take these warnings seriously. The annual societal cost of FGH_1AI-associated sedation, leading to impairment and accidents, has been estimated as $US11.3 billion versus the total societal benefit of treatment being $US7.7 billion (26), though these estimates are based on assumptions and, therefore, are subject to uncertainty.

FGH_1AIs are frequently used to treat seasonal allergic rhinitis and the common cold, and these conditions can be extremely debilitating and may significantly impair the quality of life. Besides the side effects of FGH_1AIs, the allergic rhinitis itself is associated with sedation (15). These pathophysiological conditions can present a serious safety concern, making it necessary for pilots to receive medical treatment. Although some FGH_1AIs—for example, diphenhydramine and promethazine—are also useful in the treatment of motion sickness (24), their use should be limited to passengers.

Several studies have compared the effects of FGH_1AIs with second-generation H_1 antagonists and found that some of the second-generation antihistaminics are free of sedation or cognitive impairment (6,16–18,28). Some of these drugs—fexofenadine, loratadine, and desloratadine—are approved by aeromedical authorities (13,23), but it is obvious from the present study that some pilots continue to take sedating first-generation antihistaminics while performing aviation duties. This practice may be partly because these pilots do not feel any sedation and, thus, consider that the drug is safe. However, one should be cautioned that there are 2 aspects of sedation—(i) sleepiness and lethargy and (ii) impairment of superior cognitive functions (15). Therefore, pilots may not even be aware of the serious effects of these drugs on their performance.

Postmortem aviation toxicological findings in the present study demonstrated that, during the 16-year period, approximately 6.4% of all pilots (5281) have had FGH_1AIs in their system. The number of FGH_1AI-associated pilot fatalities was higher in the general aviation category than in any other operation categories, which is consistent with the observations reported earlier (1,7,25). Of the 338 antihistamine-associated pilot fatalities, 69.5% of pilots also had other drug(s) and/or ethanol in their system. Some of the drugs—atropine, lidocaine, and analgesics—found in the pilots could have been administered by emergency health care providers at accident scenes or at hospitals for resuscitation, pain reduction, and/or surgical procedures. Whereas, other drugs—for example, antidepressants, cardiovascular agents, sympathomimetics, and even abused drugs—and ethanol were very likely present in the system of the pilots prior to the accidents. The presence of CNS-affecting substances, along with FGH_1AIs, suggests concurrent use of these substances, thereby additively impairing motor skills (24,27).

Therapeutic blood and/or plasma (serum) concentration ranges of brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, and triprolidine are reported to be 5–17, 8–40, 8–112, 69–138, 10–89, 2–99, and 4–85 ng·mL–1, respectively (4,14). The relationship between the plasma (serum) and the whole blood concentrations of all of the 8 antihistaminics is not known, and the plasma (serum) to blood concentration ratio of an antihistamine may not necessarily be equivalent to 1. For example, the plasma to blood concentration ratios of chlorpheniramine, diphenhydramine, and promethazine are reported to be 0.83, 1.3, and 1.5, respectively (14). Also, depending upon the postmortem interval, there is the potential for postmortem redistribution of the antihistamines (2,21), thereby altering their blood concentrations after the fatal accident. The presence of other drugs and/or ethanol in the fatalities may further affect the distribution of antihistamines; thus, their blood concentrations may be different in relation to situations when an individual is exposed to only 1 antihistamine. Therefore, the blood antihistamine concentrations found in the present study may not truly represent their antemortem plasma (serum) levels. Toxic and lethal concentrations of FGH_1AIs in whole blood are not clearly established based on the postmortem forensic toxicology of death investigation cases, though the lowest blood concentrations determined to have resulted in death were 200 ng·mL–1 for brompheniramine; 500 ng·mL–1 for chlorpheniramine; 5000 ng·mL–1 for diphenhydramine; 700 ng·mL–1 for doxylamine; 1900 ng·mL–1 for pheniramine; and 2400 ng·mL–1 for promethazine (4,14)

Although the NTSB has determined the use of FGH_1AIs as the probable cause or a contributing factor in at least 18.6% of the 338 antihistamine-related accidents, the final reports of 2.4% of the accidents are not yet available in the public domain database. As those reports are finalized, the number of accidents may increase wherein the use of an FGH_1AI by pilots was the probable cause or a contributing factor. In 8 accidents wherein FGH_1AIs were involved, the use of ethanol or other CNS depressants by pilots was mentioned by the NTSB as the cause or a factor. However, since antihistamines were also present in these fatalities, the potential interactive effects of these substances (CNS depressants and antihistamines) on impairing cognitive functions cannot be ruled out. Additionally, even if drugs were not determined as the cause or a factor in an accident, they still had subtle effects on cognitive functions. For example, in a fatality where tetrahydrocannabinol carboxylic acid and chlorpheniramine were found to be present, the NTSB determined the probable cause of this accident as "The pilot's failure to maintain clearance from electrical power lines."

Ideally, considering the prohibition for the use of the antihistaminics by civilian aviators, a sedating antihistamine should not have been found in any pilot fatality. The antihistamine-involved pilots were identified only because they were victims of fatal accidents and their postmortem samples were toxicologically evaluated. Even though contributing roles of other factors—for example, weather conditions, mechanical deficiencies, and/or piloting errors—cannot be completely ruled out in the 338 accidents, this number is of concern to aviation safety, particularly when there is an overall increasing trend in the prevalence of FGH_1AI-associated fatal aviation accidents.

CONCLUSION

Although sedating antihistamines are prohibited and there are alternative drugs available that are safe to use during aviation duties, there is an increasing trend in the use of FGH_1AIs by civilian pilots. To prevent this problem from becoming more serious in the future, more emphasis should be given to controlling the use of the antihistaminics by civil aviators. It would be beneficial to educate and alert aviators during their flight training and medical examinations, with real-life examples of the adverse effects of antihistamines and associated unwanted serious outcomes.

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