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Benzodiazepine Use in Pilots of Civil Aviation Accidents: 1990-2008 Toxicology and Autopsy Findings

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16. Abstract

Introduction: Benzodiazepine medications have a long history of abuse. They are categorized as central nervous system depressants, and there are currently 15 different benzodiazepines prescribed in the United States and an additional 20 in other countries. The side effects of these medications include drowsiness, dizziness, decreased alertness, and/or memory loss, which can lead to impairment and a decreased ability to properly control an aircraft. The presence of these medications in postmortem specimens of aviation accident victims can help determine the cause of the accident and, potentially, result in serious legal consequences. Our laboratory is in a unique position because a medical history is available to investigators for most certified pilots. With this in mind, we compared benzodiazepine compounds found following postmortem analysis with the available medical history for each victim. This evaluation was conducted to determine if these records supported the use of such medications or if the aviators were taking the compounds without the approval of their aviation medical examiners or possibly abusing the substances. In addition, a medical review of the autopsy records was also conducted. **Method:** Toxicological information from analyses was retrieved from the Civil Aerospace Medical Institute's (CAMI's) Forensic Toxicology Research Laboratory database. Case histories and accident information were obtained from the National Transportation Safety Board. Medical histories were obtained from the FAA's medical certification database and CAMI's autopsy team database. **Results and Discussion:** Over the examined time period (1990-2008), there were 6,062 fatal aviation accident cases received at CAMI, and 96 (~1.6%) pilots were found positive for a benzodiazepine. In ~74% of pilots found positive for benzodiazepine(s), it was determined that another compound was detected and more than one additional compound was often present. Fatal aviation accidents involving pilots who had taken a benzodiazepine compound prior to the flight are an infrequent event; however, concomitant use of more than one compound with benzodiazepines is common. This study highlights the use of benzodiazepine over the examined time period in the pilot community and presents a variety of demographic information about the pilots involved in such accidents.

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CONTENTS

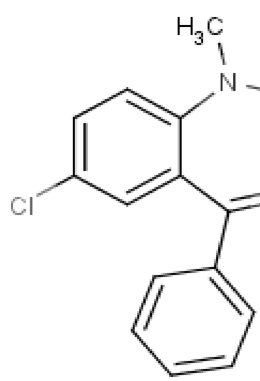
Benzodiazepine Use in Pilots of Civil Aviation Accidents: 1990-2008 Toxicology and Autopsy Findings

INTRODUCTION

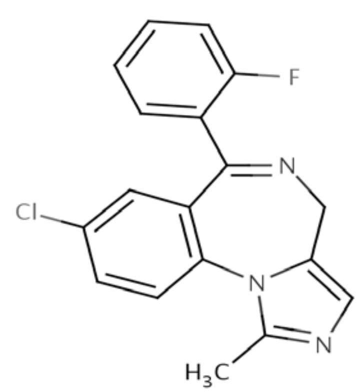
Benzodiazepine medications have a long history of abuse due primarily to the extensive abuse potential of these drugs. They fall into the category of central nervous system (CNS) depressants, and currently, 15 different benzodiazepines are prescribed in the United States and an additional 20 in other countries.[1] Benzodiazepines are used therapeutically to produce sedation, induce sleep, relieve anxiety/panic disorders and muscle spasms, and to prevent seizures by slowing the central nervous system.[2-4] The side effects of these medications include drowsiness, dizziness, decreased alertness, and/or memory loss, all of which can lead to diminished ability to properly control an aircraft.[5,6] In addition, benzodiazepines are commonly used in high doses by polydrug abusers, alcoholics, and sometimes as primary recreational drugs. Usually, these compounds enhance and prolong the "high" obtained from other drugs, including heroin, other opioids, cocaine, and amphetamines.[7] Determining the presence of these medications in postmortem specimens of aviation accident victims can help determine the cause of the accident and, potentially, result in serious legal consequences. The use of these medications by pilots is prohibited by the Federal Aviation Administration (FAA). For this reason, specimens from each pilot fatality received by the forensic toxicology laboratory at the Civil Aerospace Medical Institute (CAMI) are analyzed for a number of benzodiazepines, including diazepam, nordiazepam, triazolam, alprazolam, temazepam, αhydroxyalprazolam, oxazepam, clonazepam, lorazepam, and midazolam.

The history of benzodiazepine use dates back to the 1960s. Chlordiazepoxide was the first to be marketed as a sedative and an anxiolytic.[2] Diazepam, marketed as Valium®, was once the most widely prescribed drug in the U.S. By the mid-1980s, there was a decrease in the number of prescriptions written as the danger of abuse became clear;[8-10] however, its illicit use has been steadily increasing and currently presents a health problem.[7,11] Nearly all available benzodiazepines have been abused, but those which enter the brain rapidly, diazepam (Valium®), for example, are preferred to those which are absorbed more slowly, such as Oxazepam (Serenid®).[7]

These compounds can be classified into first- and second-generation benzodiazepines. Diazepam (Valium®) falls into the first-generation group with a basic three-ring structure, and midazolam, which falls into the second-generation group of benzodiazepines with a four-ring system (Figure 1). Furthermore, benzodiazepines are sub-classified based on the elimination half-life of the compound and any pharmacologically active metabolites: ultra-short acting (e.g., triazolam), short acting (half-life of < 6 hours, e.g., midazolam), intermediate (half-life of 6 to 24 hours, e.g., oxazepam), and long acting (half-life > 24 hours, i.e. diazepam).[2, 12, 13]



diazepam



midazolam

Figure I. Chemical structures of a first-generation (diazepam) and a second-generation (midazolam) benzodiazepine.

Nearly all benzodiazepines are extensively absorbed when taken orally. A proportion of these undergo biliary recirculation and are metabolized, then excreted into bile, followed by reabsorbtion back into the blood. The long half-lives seen in many of these compounds can be attributed to protein binding, biliary recirculation, and fat storage.[2] As already stated, benzodiazepines have many adverse effects, all of which would be incongruent with the operation of an aircraft. In combination with other drugs that depress the CNS, such as alcohol, this effect is even more harmful due to their synergistic effect.

Our laboratory is in a unique position because a medical history for most certified pilots is available to investigators. With this in mind, we compared the benzodiazepine compounds found following postmortem analysis with the available medical history for each victim. Although these compounds are not allowed per current FAA regulations,[14] this evaluation was conducted to determine if the aviator's medical history supported the use of such medications or if the aviator was taking the compound without the knowledge of his/her aviation medical examiner, or was possibly abusing the substance.

METHODS

The CAMI Forensic Toxicology Research Laboratory evaluates postmortem samples collected from pilots involved in civil aviation accidents. Toxicological information and a case history for each case involving benzodiazepines were obtained from CAMI's toxicology database. Our laboratory gathered information on all benzodiazepine-positive civil aviation fatalities that were received between 1990 and 2008 (19-year period). The National Transportation Safety Board (NTSB) is the primary federal agency responsible for investigating and determining the probable cause(s) or factor(s) involved in civil aviation accidents. Accident information and probable cause(s) of aviation accidents were obtained from the NTSB's online database (www.ntsb.gov/ntsb/query.asp). The aviator's medical history was obtained from the FAA's Document Information Workflow System (DIWS). Data analysis was performed using the statistical software package, SPSS V.18 (SPSS Inc., Chicago, IL).

RESULTS AND DISCUSSION

Epidemiology

Over the 19-year period (1990-2008), specimens from 6,112 aviators involved in fatal aviation accidents were received at CAMI for analysis. During this time period, there were 96 aviation accidents involving a benzodiazepine-positive pilot (Figure II). Benzodiazepine-positive pilots accounted for approximately 1.6% of all fatal aviation accidents received during this time period. Of these 96 accidents, only two were not investigated by the NTSB. The NTSB listed the use of drug(s) as

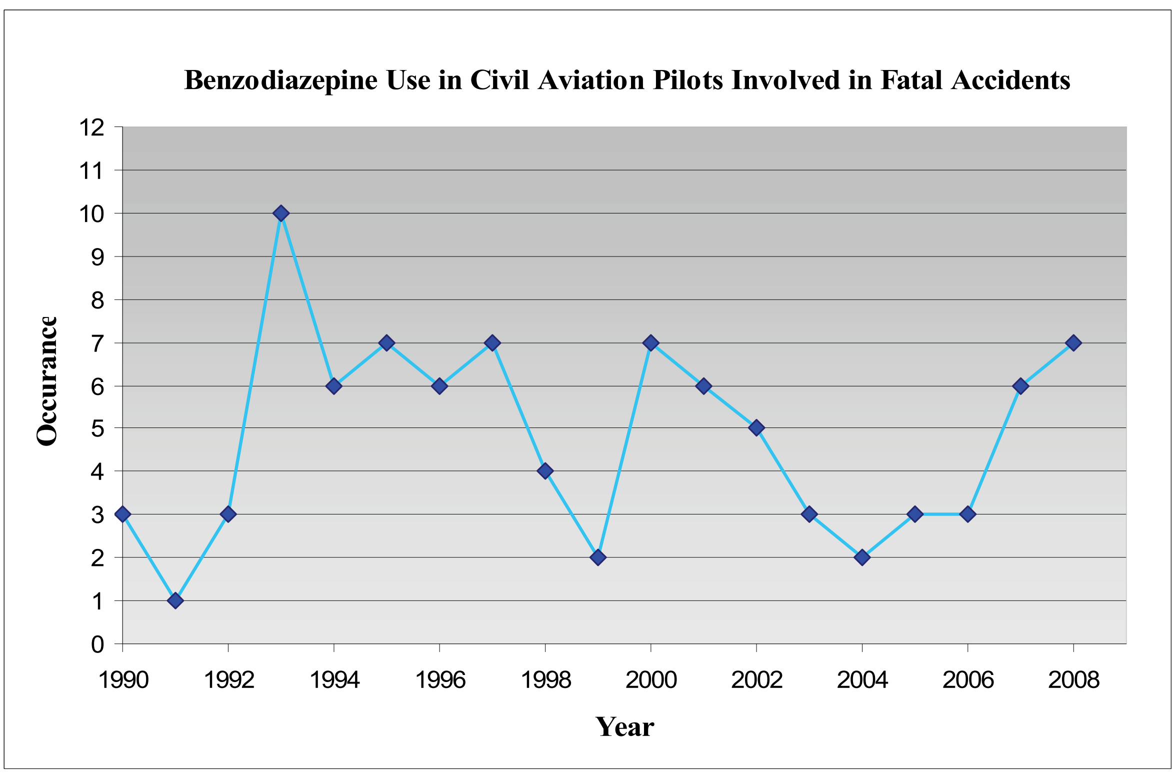


Figure II. Benzodiazepine-positive pilots involved in fatal accidents over the examined time period.

the probable cause of the fatal incident in 14 of the 96 (~15%) cases that they investigated (Table I). The NTSB listed benzodiazepines as a factor in 21 (~23%) of these accidents (Table I).

Private pilot licenses were held by 53 (55%) of the aviators, 22 (23%) were licensed commercial pilots, nine (9%) were student pilots, eight (8%) were licensed airline transport pilots, and four (4%) were not licensed pilots (Table III). The majority of pilots, 49 (~54%), held a class-3 medical certificate (Table IV). Class-2 medical certificates were held by 25 (~28%) aviators and class-1 medical certificates were held by only six (~7%) pilots (Table IV). Of the remaining individuals, either they had been denied certification due to not meeting the required state of health needed to hold a pilot's license, were pending certification, or not medically certified to fly.

Eighty-nine (~93%) of the 96 fatal accidents were operated as general aviation, Title 14 of the Code of Federal Regulations (CFR) Part 91, two (~2%) were operated as ultralight flights (14 CFR Part 103), one (~1%) was operated as air taxi/commercial (14 CFR Part 135), two (~2%) were operated as agricultural flights (14 CFR Part 137), and two (~2%) were not investigated by the NTSB (Table III). Of the 96 pilots that tested positive for benzodiazepines, 94 (98%) were male and two (2%) were female. The most alarming statistic obtained from this study was the high number of poly-pharmacy (cases positive for more than one potentially impairing substance) cases found. In fact, 68 (~71%) of the 96 pilots involved in these accidents were found to be positive for an additional potentially impairing substance along with the benzodiazepine(s) (Table I).

Toxicology

The following benzodiazepines were detected in the 96 aviators in question over the examined time period, along with the number of occurrences for each: nordiazepam (60), diazepam (36), temazepam (29), αhydroxyalprazolam (13), midazolam (12), alprazolam (9), and chlordiazepoxide (4). Along with the detected benzodiazepines, ethanol was found in 21 (~22%) of these pilots. Blood ethanol concentrations ranged from 21–173 mg/dL in these cases, and in each case it was determined that the ethanol detected was from consumption and not postmortem ethanol formation by microbial action. Fourteen of the 21 ethanol-positive cases tested higher than the FAA's legal limit of 40 mg/dL. Multiple aviators tested positive for ethanol above 100 mg/dL, indicating significant impairment. In addition to benzodiazepines and ethanol, numerous other compounds were detected in these 96 cases (Tables I, II). Many of these compounds, when taken concomitantly with a benzodiazepine, could increase the pilot's risk of injury or death due to a drug-related incident during flight.

DIWS Medical History

Of the 96 pilots that were found positive for benzodiazepines, 72 (75%) had reported to their aviation medical examiner that they were not taking any prescription or over-the-counter (OTC) medications. The remaining 24 pilots had reported the use of some type of medication to their aviation medical examiner. Ten of these 24 pilots had reported the use of a relatively benign compound for the treatment of hypertension or a cholesterol-lowering drug. Four aviators reported the use of pain-relieving agents such as acetaminophen, aspirin, sumatriptan, and meloxicam. Documented medical issues, either ongoing or in the pilot's past, were found in the medical history documentation for 41 of these victims (~43%). Of these individuals, 12 had medical conditions concerning the heart or suffered from hypertension. Hernia was the next most common medical issue reported involving eight pilots. Unspecified neurotic disorders were documented in six aviators. Migraine headaches, allergic conditions, urinary tract disorders, and diabetes were noted in the remaining 15 aviators. Of the 21 ethanol-positive aviators, eight had previous alcohol-related offenses listed in their medical record, of which two had multiple offenses.

The statistics from the benzodiazepine-positive pilots draw attention to two important issues within the aviation community. First, the vast majority of the pilots in this study had not reported taking, or being prescribed, any medication to their aviation medical examiner prior to the fatal accident. Second, a majority of the pilots in this study had taken more than one medication prior to the fatal accident, with one of these medications being an impairing benzodiazepine. This practice is especially dangerous prior to flight because of the potential for a multiplication of any negative side effect of each compound taken.

Autopsy Analysis

A total of 29 autopsy reports from this group of 96 pilots found positive for benzodiazepines and possibly other drugs was received at CAMI during this period. One autopsy reported a recent myocardial infarction in a 54 year-old pilot with a previous alcohol offense. The most common pathological conditions reported in the autopsies of these 29 aviators were: 1) coronary artery disease (CAD) in 13 cases (49%); 2) cardiomegaly and ventricle hypertrophy, each reported in six cases (21%), respectively; 3) fatty liver in six cases (21%); and 4) nephrosclerosis

Table I. NTSB cause or factor determination, medical history, and compounds detected through toxicological analysis.

Pilot	Drug Use as a Cause/Factor as Determined by NTSB	Reported Medications	Medical History	Benzodiazepine(s)	Other Compounds
1	Factor	—	Allergies	diazepam, nordiazepam	fenfluramine, diphenhydramine
2	Cause	—	Hernia, Alcohol offense	nordiazepam	ethanol
3	Factor	—	Emphysema, Hypertension	diazepam, nordiazepam	acetaminophen, chlorpheniramine, pseudoephedrine
4	Possible Factor	—	—	temazepam	fluoxetine, norfluoxetine
5	Cause	—	Hypertension	nordiazepam	ethanol, chlordiazepoxide
6	Cause	—	—	alprazolam, α-hydroxyalprazolam	ethanol
7	Factors	—	—	temazepam, oxazepam	quinine
8	Cause	—	—	diazepam, nordiazepam	ethanol, marijuana, cocaine, hydrocodone, hydromorphone, oxazepam, acetaminophen
9	Cause	—	Alcohol offense	nordiazepam, oxazepam, temazepam	fenoprofen
10	Factor	—	—	alprazolam, α-hydroxyalprazolam	pentazocine
11	Cause	—	—	diazepam, nordiazepam, temazepam	ethanol, marijuana, butalbital, salicylate
12	Cause	—	—	diazepam, nordiazepam, temazepam	—
13	Cause	—	—	alprazolam, diazepam, nordiazepam, α-hydroxyalprazolam, oxazepam, temazepam	marijuana, salicylate
14	Factor	—	—	diazepam, nordiazepam	hydrocodone, dihydrocodeine
15	Cause	—	—	diazepam, nordiazepam, oxazepam	marijuana, amphetamine, methamphetamine
16	Cause	Y*	Multiple alcohol offenses	nordiazepam, diltiazem	ethanol, fluoxetine, norfluoxetine, chlorpheniramine, ephedrine, phenylpropanolamine, acetaminophen, salicylate, chlordiazepoxide, pseudoephedrine
17	Factor	—	Ulcer	diltiazem, nordiazepam, temazepam, oxazepam	desipramine, imipramine, diphenhydramine, acetaminophen
18	Cause	Y*	Hypertension	diazepam, nordiazepam	chlorpheniramine, diphenhydramine

*Compounds Not Specified

Table I (continued). NTSB cause or factor determination, medical history, and compounds detected through toxicological analysis.

Pilot	Drug Use as a Cause/Factor as Determined by NTSB	Reported Medications	Medical History	Benzodiazepine(s)	Other Compounds
19	Cause	Y*	Heart-related conditions	chlordiazepoxide, diazepam, nordiazepam, oxazepam, temazepam	amitriptyline, nortriptyline, atenolol, diltiazem
20	Cause	—	—	alprazolam, α-hydroxyalprazolam	marijuana, dihydrocodeine, hydrocodone, hydromorphone, acetaminophen
21	Factor	—	—	oxazepam, nordiazepam, chlordiazepoxide, norchlordiazepoxide	diphenhydramine, propranolol, acetaminophen
22	Factor	—	—	diazepam, nordiazepam, temazepam	buspirone, oxymetazoline, acetaminophen
23	Factor	—	Drug abuse, Disease of the blood	nordiazepam	phenobarbital, tramadol, pseudoephedrine, phenylpropanolamine, chlorpheniramine
24	Cause	—	—	α-hydroxyalprazolam	marijuana, meperidine, metoprolol
25	Factor	—	—	oxazepam, temazepam	cocaine, metoprolol, acetaminophen
26	Factor	—	—	diazepam, nordiazepam, temazepam, oxazepam	—
27	Factor	Doxazosin, Triamterene	Hypertension, Atherosclerosis, Ulcer, Skin disorder	alprazolam, α-hydroxyalprazolam	triamterene, acetaminophen
28	Factor	Atorvastatin	Musculoskeletal disorder, Abnormal blood chemistry	temazepam, nordiazepam, oxazepam, diazepam	propranolol
29	Factor	Sumatriptan	Skin disorder, Migraine, Mononeuritis, Developmental learning difficulites	alprazolam, α-hydroxyalprazolam, nordiazepam, oxazepam	acetaminophen, citalopram, desmethylvenlafaxine, hydrocodone, hydromorphone, venlafaxine
30	Factor	—	—	diazepam, nordiazepam	—
31	Factor	—	—	alprazolam, α-hydroxyalprazolam	butalbital, hydrocodone, dihydrocodeine, hydromorphone, propoxyphene, norpropoxyphene, acetaminophen
32	Factor	Tamsulosin, Meloxicam	Aphakia, Alcohol offense	diazepam, nordiazepam, oxazepam, temazepam	ethanol, cyclobenzaprine, amitriptyline, nortriptyline

*Compounds Not Specified

Table II. Compounds detected in pilots in addition to benzodiazepines.

Opioids-40, Barbiturates-4, Anesthetics-9 THC-19, Cocaine-5, Amphetamines-3	**Antidepressants/Anxiolytics-38, Anticonvulsants-1**	**Anticholinergics-3, Antiemetics-1, Antihistamines-2, Anti-Obesity-3, Anti-Malarials-5**	**Alpha/Beta/Calcium Channel Blockers-15, Antihypertensive-1, Diuretics-1, Proton-Pump Inhibtors-1, Sympathomimetic-1**	**OTC Cold Medications-47**	**OTC Pain Relievers-37**
Morphine	Phenytoin	Atropine	Atenolol	Phenylpropanolamine	Salicylate
Fentanyl	Fluoxetine	Metoclopramide	Metoprolol	Dextrorphan	Naproxen
Pentazocine	Bupropion	Fenfluramine	Propranolol	Dextromethorphan	Acetaminophen
Dihydrocodeine	Cyclobenzaprine	Phentermine	Triamterene	Ephedrine	Fenoprofen
Hydromporphone	Paroxetine	Quinine	Omeprazole	Pseudoephedrine	Ibuprofen
Meperidine	Venlafaxine	Ranitidine	Naphazoline	Cetirizine	
Hydrocodone	Citalopram		Diltiazem	Diphenhydramine	
Propoxyphene	Butalbital		Verapamil	Chlorpheniramine	
Tramadol	Trazodone		Doxazosin	Triprolidine	
Lidocaine	Desipramine		Reserpine	Brompheniramine	
Etomidate	Imipramine				
Phenobarbital	Amitriptyline				
Butalbital	Sertraline				
Marihuana	Mirtazapine				
Cocaine	Buspirone				
Amphetamine	Lamotrigine				

Table III. Flight categories and airman flying ratings for benzodiazepine-positive pilots.

	Airman Flying Ratings*			
Flight Categories*	Student	Private	Commercial†	Airline Transport
General Aviation (14 CFR Part 91)‡	8	53	19	7
Air Taxi and Commuter (14 CFR Part 135)	—	—	—	1
Ultralight Vehicle (14 CFR Part 103)§	1	—	—	—
Agricultural (14 CFR Part 137)	—	—	2	—

* One accident involved a pilot who did not hold a medical certificate nor was the accident investigated by the National Transportation Safety Board.

† One commercial pilot was involved in an aviation accident not investigated by the National Transportation Safety Board.

‡ Two pilots did not hold medical certificates.

§ One pilot did not hold a medical certificate.

Table IV. Airman medical certificate categories and flying ratings for benzodiazepine-positive pilots.

	Airman Flying Ratings*		
Medical Certificate Categories*	**First-Class**	**Second-Class**	**Third-Class**
Airline Transport	4	4	—
Commercial†	1	15	5
Private‡	1	5	38
Students§	—	1	6

* Four victims did not hold medical certificates.

† One commercial pilot's medical certificate had been denied.

‡ Two private pilots' medical certificates were pending and two had been denied.

§ Two student pilots' medical certificate had been denied.

in five cases (17%). Except the fatty liver condition, the age group distribution for the above-reported conditions was observed as follows: 1) CAD most common in pilots older than 50 (55%); 2) both cardiomegaly and ventricle hypertrophy in the > age 60 groups (31% each); and 3) nephrosclerosis was most common in pilots older than 50 (17%). This distribution was expected, as these conditions are typically more prevalent in older subjects.

CONCLUSIONS

Fatal aviation accidents involving a pilot who had taken a benzodiazepine compound prior to flight were infrequent events, comprising only 1.6% (96 of 6,062) of cases received at CAMI over the 19-year period examined. In ~71% of the pilots found positive for a benzodiazepine(s), at least one additional compound was detected, and often more than one compound was present. In only 18 of the 96 aviators (~19%) was there a documented condition in their medical records, such as a previously established mental condition, that would potentially warrant the use of a benzodiazepine. This demonstrates that the majority of the aviators evaluated in this study (~81%) were taking a benzodiazepine medication without the knowledge of their aviation medical examiner. As related to the most common benzodiazepines found in postmortem specimens from aviation accident victims, the results of the present study are consistent with a previous study conducted at CAMI by Canfield et al. (15), in which it was determined that diazepam, nordiazepam, alprazolam, temazepam, and chlordiazepoxide were the most frequently detected benzodiazepine medications in aviators. Midazolam was the most common benzodiazepine found in the present study, as compared to the previous CAMI study. These findings demonstrate the need for pilots to disclose all medications being taken to their aviation medical examiner and avoid taking multiple medications simultaneously due to unforeseen complications from a multiplication of negative side effects.

REFERENCES

1. www.Justice.Gov/Dea/Concern/Benzodiazepines. (February 2010).
2. Fenton, J.J. Toxicology: A Case Oriented Approach. (CRC Press, Boca Raton, FL, 2002).
3. Hoffman, E.J. and Mathew, S.J. Anxiety Disorders: A Comprehensive Review of Pharmacotherapies. *Mt Sinai J Med,* 75: 248-62 (2008).
4. Lader, M. Effectiveness of Benzodiazepines: Do They Work or Not? *Expert Rev Neurother,* 8: 1189-91 (2008).
5. Mills, K.C., Spruill, S.E., Kanne, R.W., et al. The Influence of Stimulants, Sedatives, and Fatigue on Tunnel Vision: Risk Factors for Driving and Piloting. *Hum Factors,* 43: 310-27 (2001).
6. Vgontzas, A.N., Kales, A., and Bixler, E.O. Benzodiazepine Side Effects: Role of Pharmacokinetics and Pharmacodynamics. *Pharmacology,* 51: 205-23 (1995).
7. Ashton, H. Drink, Drugs and Dependence. (Routledge, London, 2002).
8. Bergman, U. and Griffiths, R.R. Relative Abuse of Diazepam and Oxazepam: Prescription Forgeries and Theft/Loss Reports in Sweden. *Drug Alcohol Depend,* 16: 293-301 (1986).
9. Elliott, L., Glenday, J., Freeman, L., et al. Reducing Diazepam Prescribing for Illicit Drug Users: A Randomised Control Study. *Drug Alcohol Rev,* 24: 25-31 (2005).
10. Mulvihill, M.N., Suljaga-Petchel, K., Falkenstein, J., et al. Patterns of Diazepam Prescribing in Primary Care: A Case Control Study. *Mt Sinai J Med,* 52: 276-80 (1985).
11. Haw, C. and Stubbs, J. Benzodiazepines—A Necessary Evil? A Survey of Prescribing at a Specialist UK Psychiatric Hospital. *J Psychopharmacol,* 21: 645-9 (2007).
12. Brunton, L.L., Lazo, J.S., and Parker, K.L., eds. Goodman & Gilman's the Phamacological Basis of Therapeutics, 11th ed. (McGraw-Hill, New York, 2006).
13. Ito, K., Yamada, Y., Nakamura, K., et al. Classification of Benzodiazepine Hypnotics in Humans Based on Receptor Occupancy Theory. *J Pharmacokinet Biopharm,* 21: 31-41 (1993).
14. Booze, C.F. Aeromedical Certification Systems Manual. Federal Aviation Administration Office of Aviation Medicine. (Oklahoma City, OK, 1985).
15. Canfield, D.V., Salazar, G.J., Lewis, R.J., et al. Comparison of Pilot Medical History and Medications Found in Postmortem Specimens. Federal Aviation Administration Office of Aerospace Medicine, Report no. DOT/FAA/AM-06/12. (Washington, DC, 2006).