



NATIONAL TRANSPORTATION SAFETY BOARD

Office of Research and Engineering
Washington, DC

MEDICAL FACTUAL REPORT

September 6, 2017

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Medical Officer

A. ACCIDENT: CEN15FA378 - Martinsville, Illinois

On August 21, 2015 at about 0730 central standard time, a Cessna 172 airplane, N8265B, registered to the pilot, collided with terrain under unknown circumstances near Martinsville, Illinois. The non-certificated pilot, who was the sole occupant, sustained fatal injuries. The flight was being conducted under the provisions of *Code of Federal Regulations* (CFR) Part 91. Visual meteorological conditions prevailed throughout the area at the time of the accident. The flight originated from 1H8 about 0700 the wreckage was found at 1500 August 22, 2015, about 30 hours after the crash.

B. GROUP IDENTIFICATION:

No group was formed for the medical evaluation in this accident.

C. DETAILS OF INVESTIGATION

Purpose

This investigation was performed to evaluate the pilot for any medical conditions, the use of medications/illicit drugs, and the presence of toxins.

Methods

The FAA medical case review, personal medical records, FAA Bioaeronautical Sciences Research Laboratory toxicology report, and autopsy report were reviewed.

FAA Medical Case Review

According to the FAA medical case review, the 63-year-old male had his only medical certification examination on March 24, 2003. At that time, the exam documented he was 69 inches tall, weighed 225 pounds, and had reported 80 hours total flight time. He reported a diagnosis of hypothyroidism treated with thyroid replacement medication. The examination did not identify any other significant medical concerns. He was issued a third class medical certificate without limitations; the certificate was no longer valid after March 31, 2005. At the time of the accident, he was operating an airplane that required both an FAA pilot certificate and a medical certificate but had neither.

Personal Medical Records

The investigation received medical records from the 63-year-old male pilot's primary care provider, nephrologist (kidney doctor), and oncologist (cancer doctor) from June 2014 to

August 2015. These records identified multiple medical conditions including: anxiety, chronic pain, Type II diabetes, chronic kidney disease, high blood pressure, hypothyroid, metastatic colon cancer, and deep venous thrombus. The pilot was receiving prescriptions from several providers. Table 1 outlines the medications identified by the investigation.

Table 1 – Pilot's Identified Prescription Medications

	Medication	Dose	Description (Trade Name)	DEA Schedule ¹
1	Alprazolam	2 mg	Sedating antianxiety medication (Xanax) ²	Schedule IV
2	XELIRI - Bevacizumab		Anticancer medication therapy ^{3,4}	N/A
3	Diphenoxylate /atropine	2.5 mg / 0.025 mg	Sedating medication for diarrhea (Lomotil) ⁵	Schedule V
4	Fentanyl Patch	25 mcg/hr	Sedating opioid pain medication (Novaplus) ⁶	Schedule II
5	Glipizide	5 mg	Oral diabetes medication (Glucotrol) ⁷	N/A
6	Levothyroxine	50 mcg	Thyroid replacement hormone (Synthroid) ⁸	N/A
7	Lisinopril	10 mg	Blood pressure medication (Zestril) ⁹	N/A
8	Metoprolol	50 mg	Blood pressure medication (Toprol) ¹⁰	N/A
9	Oxycodone	15 mg	Sedating opioid pain medication (Oxycontin) ¹¹	Schedule II

¹ The Drug Enforcement Agency identifies drugs and other substances that are considered controlled substances under the Controlled Substances Act and divides them into five schedules. Substances are placed in their respective schedules based on whether they have a currently accepted medical use in treatment in the United States, their relative abuse potential, and likelihood of causing dependence when abused. Schedule II substances have a high potential for abuse while schedule V substance have a low potential for abuse.

² National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. XANAX- alprazolam. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=388e249d-b9b6-44c3-9f8f-880ecced0239f> Accessed 08/04/2017

³ National Institutes of Health. National Cancer Institute. Cancer Treatment 2017. XELIRI. <https://www.cancer.gov/about-cancer/treatment/drugs/XELIRI> Accessed 08/25/2017

⁴ National Institutes of Health. National Cancer Institute. Cancer Treatment 2017. Bevacizumab <https://www.cancer.gov/about-cancer/treatment/drugs/bevacizumab> Accessed 08/25/2017

⁵ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. LOMOTIL- diphenoxylate hydrochloride and atropine sulfate. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f170584a-1072-4fd7-b1dc-6756703483b9> Accessed 08/25/2017

⁶ National Institute of Health, U.S. Library of Medicine *DailyMed* 2017. FENTANYL - NOVAPLUS- fentanyl patch <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9baf2912-9d0f-412a-8fbf-617f6a4f91ed> Accessed 08/25/2017

⁷ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. GLUCOTROL- glipizide. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b4f55916-91a2-4171-a361-919e7cb329b0> Accessed 08/04/2017

⁸ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. SYNTHROID- levothyroxine. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e11ad30-1041-4520-10b0-8f9d30d30fcc> Accessed 08/04/2017

⁹ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. ZESTRIL- lisinopril. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=46f17ba7-a78c-4a9e-7597-27654f097bd3> Accessed 08/04/2017

¹⁰ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. TOPROL XL- metoprolol. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4a5762c6-d7a2-4e4c-10b7-8832b36fa5f4> Accessed 08/04/2017

¹¹ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. OXYCONTIN- oxycodone. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bfdfe235-d717-4855-a3c8-a13d26dadede> Accessed 08/04/2017

According to available records, his most recent health care visit was to his nephrologist for evaluation of chronic kidney disease on August 04, 2015 (about three weeks before the accident). At that time, he was not feeling tired or poorly and did not complain of any neurologic or mood disorder. The pilot's height was recorded as 69 inches, weight as 215 pounds, and BMI as 31.7 kg/m². The physician documented the pilot's chronic medical conditions and kidney disease, and did not identify any new concerns.

An earlier visit to his primary care provider, dated July 23, 2015, (about one month before the accident) was for routine follow up of his medical conditions. At that time, the pilot's diabetes was controlled with oral medications and his metastatic cancer showed improvement (tumor shrinkage) on a recent cancer scan. During the visit, the pilot denied any neurologic symptoms including difficulty with concentration, poor balance, headaches, disturbances in coordination, numbness, inability to speak, falling, tingling, brief paralysis, visual disturbances, seizures, weakness, sensation of room spinning, tremors, fainting, excessive daytime sleeping or memory loss. He also denied any significant psychiatric concerns including no sense of great danger, anxiety, thoughts of suicide, mental problems, depression, thoughts of violence and frightening visions or sounds. However, he did complain of joint pains and arthritis. The physical examination did not identify any significant abnormal findings. The physician documented the chronic problems were controlled with current medications but added a prescription for fentanyl patches every 72 hours for pain management.

The pilot's most recent visit to his oncologist was on July 7, 2015 (six weeks before accident). On physical examination, the physician assistant providing care commented that patient insight and judgment were normal, and that recent and long-term memory were normal for age.

Autopsy

According to the Terre Haute Indiana Regional Hospital Department of Pathology autopsy report, the cause of death was blunt force trauma.¹² The Clark County Illinois Coroner determined the cause of death was blunt force trauma and the manner was accident. The autopsy did not identify evidence of metastatic tumors or any other significant natural disease.

Toxicology

AIT Forensic Toxicology Laboratory conducted testing of blood and urine as part of autopsy testing. The autopsy documented cavity blood, liver and urine specimens were submitted for testing. Blood testing detected alprazolam at 129 ng/ml, codeine at 26.4 ng/ml, diphenhydramine at 159 ng/ml, ethanol at 0.047% weight/volume, fentanyl at 3.6 ng/ml, oxycodone at 428 ng/ml, and its active metabolite oxymorphone at 19.3 ng/ml. Carbon monoxide was below the 5% reporting cutoff. Urine testing was negative for alcohol but positive for alprazolam, fentanyl and its metabolite norfentanyl, codeine and its active metabolite morphine, oxycodone and its active metabolite oxymorphone. The identified medications are described below in the description of medications detected by toxicology.

¹² According to the autopsy, the pilot had a number of possible medical conditions including cancer and the neurodegenerative disorder amyotrophic lateral sclerosis (ALS). A review of medical records identified the cancer but no evidence of ALS.

FAA Bioaeronautical Research Sciences Laboratory toxicology testing was limited to bile and liver specimens.¹³ Testing detected ethanol at 20 mg/hg in liver. Additionally, the following drugs were detected: codeine at 0.209 ug/ml in bile and at 0.03 ug/g in liver and its metabolite morphine in liver and at 0.446 ug/ml in bile, diphenhydramine in bile and liver, hydrocodone at 0.057 ug/ml in bile, metoprolol in liver, oxycodone at 0.409 ug/ml in bile and at 0.282 ug/g in liver, and its metabolite oxymorphone in bile and liver.

Description of Medications Detected by Toxicology Testing

Alprazolam is an impairing central nervous system (CNS) sedative benzodiazepine medication available as a Schedule IV controlled substance used to treat anxiety disorder and panic disorder. It is commonly marketed with the name Xanax. The drug information includes this instruction to providers: "Because of its CNS depressant effects, patients receiving alprazolam tablets should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle."¹⁴ The usual therapeutic dose range is between 60 and 200 ng/ml; levels above 100 ng/ml are considered toxic.¹⁵ With regular use, patients may develop tolerance to some of the effects of benzodiazepines and require increasing doses to achieve the same results.¹⁶ Blood alprazolam levels in 430 impaired drivers averaged 90 ng/ml and ranged up to 3,900 ng/ml.¹⁷

Codeine is a Schedule III opioid pain medication used to treat pain and decrease coughing; its active metabolite is morphine. It is a potent impairing CNS sedative and drug information includes this instruction to providers: "[acetaminophen] with codeine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of [acetaminophen] with codeine and know how they will react to the medication."¹⁸ Codeine is metabolized to morphine and norcodeine, its half-life ranges from 1.2 to 3.9 hours and accepted therapeutic levels range from about 60 to 470 ng/ml.¹⁹ With regular use, patients may develop tolerance to the effects of opioids and require increasing doses to achieve the same results.²⁰

¹³ Specimens are analyzed using immunoassay, chromatography, GC/MS, HPLC/MS, or GC/FTIR. Concentrations (ug/mL) at or above those in () can be determined for, but not limited to, the following drugs: amphetamines (0.010), opiates (0.010), marijuana (0.001), cocaine (0.020), phencyclidine (0.002), benzodiazepines (0.030), barbiturates (0.060), antidepressants (0.100), and antihistamines (0.020). Drugs and/or their metabolites, that are not impairing or abused, may be reported from the initial tests. See the CAMI Drug Information Web Site for additional information (<http://jag.camii.jccbi.gov/toxicology/>)

¹⁴ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. Alprazolam. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2238e083-08f2-0aa8-59b7-16b6d68dbd48> Accessed 1/17/2017.

¹⁵ Federal Aviation Administration. CAMI Toxicology Drug Information. Alprazolam. <http://jag.camii.jccbi.gov/toxicology/DrugDetail.asp?did=5> Accessed 1/17/2017.

¹⁶ Vinkers CH, Olivier B. Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABAA Receptor Modulators? *Adv Pharmacol Sci*. 2012

¹⁷ Baselt RC *Disposition of Toxic Drugs and Chemicals in Man*, 10th Edition. Alprazolam. Pages 74-76. Copyright 2014, Biomedical Publications, Seal Beach, California.

¹⁸ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. *TYLENOL WITH CODEINE*-acetaminophen and codeine. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=936e481e-f46c-4e03-b8e3-25961cda1909> Accessed 08/07/2017

¹⁹ Baselt RC *Disposition of Toxic Drugs and Chemicals in Man*, 10th Edition. Codeine. Pages 516-520. Copyright 2014, Biomedical Publications, Seal Beach, California.

²⁰ Dumas EO, Pollack GM. Opioid Tolerance Development: A Pharmacokinetic / Pharmacodynamic Perspective *AAPS J*. 2008

Diphenhydramine is a sedating antihistamine used to treat allergy symptoms and as a sleep aid. It is available over the counter under the trade names Benadryl and Unisom and carries the following FDA warning: may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery). The therapeutic range for diphenhydramine is about 25 to 112 ng/ml.²¹ Blood concentrations following a single dose of 50 mg diphenhydramine in 10 healthy adults produced an average peak plasma concentration of 66 ng/mL at 2.3 hours.²² Compared to other antihistamines, diphenhydramine causes marked sedation; this is the rationale for its use as a sleep aid. Altered mood and impaired cognitive and psychomotor performance may also be observed. In fact, in a driving simulator study, a single 50 mg dose of diphenhydramine impaired driving ability more than a blood alcohol concentration of 0.100.²³

Ethanol is primarily a CNS depressant commonly found in beer, wine, and liquor. After ingestion and absorption, ethanol is quickly distributed throughout the body's tissues and fluids fairly uniformly. The distribution pattern parallels the water content and blood supply of each organ. It is also produced after death by microbial activity but the vitreous and urine are less susceptible to this production.²⁴ Ethanol was detected in the blood and liver but it was not detected in the urine. This indicates the ethanol identified in this case was from post mortem production rather than ingestion.

Fentanyl is a Schedule II synthetic opioid pain medication. It is a potent impairing CNS sedative and drug information includes this instruction to providers: "[Fentanyl] may impair the mental or physical abilities needed to perform of potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of [fentanyl] and know how they will react to the medication."²⁵ Its half-life ranges from 3 to 12 hours and its therapeutic range is from 0.3 to 3.8 ng/ml.²⁶ With regular use, patients may develop tolerance to the effects of opioids and require increasing doses to achieve the same results.

Hydrocodone is a potent impairing Schedule II synthetic narcotic pain medication marketed under various names including Lortab and Norco.²⁷ It was detected in the bile but not in the blood or urine.

Metoprolol is a medication used to treat high blood pressure described in table 1. It is generally not considered impairing.

Oxycodone is a potent impairing Schedule II synthetic narcotic pain medication marketed under various names including Percocet and Oxycontin. It carries a number of warnings

²¹ FAA, Civil Aerospace Medical Institute. Toxicology Drug Information: Diphenhydramine.

<http://jag.cami.jccbi.gov/toxicology/DrugDetail.asp?did=50> Accessed 10/21/2016.

²² Baselt RC Disposition of Toxic Drugs and Chemicals in Man, 10th Edition. Diphenhydramine. Pages 684-687 Copyright 2014, Biomedical Publications, Seal Beach, California.

²³ Weiler JM, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa Driving Simulator. *Ann Intern Med.* 2000;132(5): 354-63.

²⁴ Federal Aviation Administration. CAMI toxicology Drug Information for: Ethanol

<http://jag.cami.jccbi.gov/toxicology/DrugDetail.asp?did=60> Accessed 4/14/2016

²⁵ National Institute of Health, U.S. Library of Medicine *DailyMed*, 2017. FENTANYL - NOVAPLUS- fentanyl patch <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9baf2912-9d0f-412a-8fbf-617f6a4f91ed> Accessed 08/25/2017

²⁶ Baselt RC Disposition of Toxic Drugs and Chemicals in Man, 10th Edition. Fentanyl. Pages 846-849. Copyright 2014, Biomedical Publications, Seal Beach, California.

²⁷ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. NORCO- hydrocodone. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aacf2d01-126d-4aab-9b2a-eee31a769150> Accessed 08/28/2017

including “Hypotension and profound sedation, coma, or respiratory depression may result if [oxycodone] is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). Additionally, warnings state the medication “...may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of [oxycodone] and know how they will react to the medication.”²⁸ Plasma concentrations following administration of normal release oxycodone (4.5 mg oxycodone hydrochloride plus 0.38 mg terephthalate) averaged 18 ng/mL (range, 9 -37) at 1 hour, 16 ng/mL at 2 hours, 9 ng/ml at 4 hours and 5 ng/mL at 8 hours. The half-life is reported to be 3 to 6 hours. Its primary active metabolite is oxymorphone. Toxic levels are considered to be above 200 ng/ml and in a case series of 117 fatalities involving use of mixed psychoactive drugs the average oxycodone level was 480 ng/ml.^{29,30} With regular use, patients may develop tolerance to the effects of opioids and require increasing doses to achieve the same results.

Interactions of Sedative Medications Detected in Blood

Alprazolam, codeine, diphenhydramine, fentanyl, and oxycodone are all potent CNS depressants that in combination are likely to enhance the CNS depressant effect of the other CNS depressants. Drug interaction guidance advises: "Avoid concomitant use of opioid analgesics [codeine, fentanyl, and oxycodone] and benzodiazepines [alprazolam] or other CNS depressants [diphenhydramine] when possible."³¹

²⁸ National Institutes of Health. US National Library of Medicine. *DailyMed*, 2017. OXYCONTIN- oxycodone hydrochloride tablet. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bfdfe235-d717-4855-a3c8-a13d26dade> Accessed 11/16/2016

²⁹ Federal Aviation Administration. CAMI toxicology Drug Information for: Oxycodone. <http://jag.cami.jccbi.gov/toxicology/DrugDetail.asp?did=94> Accessed 08/08/2017

³⁰ Baselt RC Disposition of Toxic Drugs and Chemicals in Man, 10th Edition. Oxycodone, pages 1528-1531 Copyright 2014, Biomedical Publications, Seal Beach, California.

³¹ Lexicomp Online®, Lexi-Comp Online™ Interaction Analysis, Hudson, Ohio: Lexi-Comp, Inc. Accessed 04/10/2017.

D. SUMMARY OF FINDINGS

The 63-year-old male pilot did not have a valid medical certificate at the time of the accident although one was required to fly the airplane involved. He had a history of multiple medical conditions including: metastatic colon cancer treated with chemotherapy, hypothyroidism, high blood pressure, diabetes controlled with oral medications, chronic pain treated with impairing opioid pain medications, and anxiety treated with an impairing benzodiazepine. Examinations within a month of the accident did not identify any significant abnormal neurologic or psychiatric findings.

The autopsy performed by the Terre Haute Indiana Regional Hospital Department of Pathology documented the pilot died from blunt force injuries but did not identify any evidence of metastatic cancer or significant natural disease.

Toxicology testing of cavity blood found the impairing medications alprazolam at 129 ng/ml, codeine at 26.4 ng/ml, diphenhydramine at 159 ng/ml, fentanyl at 3.6 ng/ml, oxycodone at 428 ng/ml and its active metabolite oxymorphone at 19.3 ng/ml and ethanol at 0.047%. Urine was negative for ethanol indicating it was from postmortem production. However, urine was positive for the impairing medications: alprazolam, fentanyl and its metabolite norfentanyl, codeine and its active metabolite morphine, oxycodone and its active metabolite oxymorphone. Additionally, the non-impairing prescription blood pressure medicine metoprolol was detected in liver. Finally, the combination of any of the opioid pain medications codeine, fentanyl, and oxycodone, the benzodiazepine alprazolam, and the sedating antihistamine diphenhydramine are likely to enhance the CNS impairing effect of the other CNS depressants.