National Transportation Safety Board
Office of Research and Engineering
Washington, DC 20594

CEN21FA230

MEDICAL

Specialist's Factual Report

August 18, 2023

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A. ACCIDENT

Location: Shreveport, Louisiana
Date: May 23, 2021

B. MEDICAL SPECIALIST

Specialist: Turan Kayagil, MD, FACEP
National Transportation Safety Board
Washington, DC

C. DETAILS OF THE INVESTIGATION

1.0 Purpose

This investigation was performed to evaluate the pilot for potentially impairing substances and potentially impairing medical conditions.

2.0 Methods

The Federal Aviation Administration (FAA) medical case review and the pilot's autopsy and toxicology reports were reviewed. Selected investigator reports and relevant regulation and medical literature were also reviewed.

D. FACTUAL INFORMATION

1.0 FAA Medical Case Review

According to the FAA medical case review, the 73-year-old male pilot's last aviation medical examination was on April 24, 2020. At that time, he reported 18,000 total civilian flight hours. He was 66 inches tall and weighed 159 pounds. He reported no medication use and no active medical conditions. No significant issues were identified and he was issued a third-class medical certificate limited by a requirement to have available glasses for near vision.

2.0 Autopsy

The pilot' s autopsy was performed by the Louisiana State University Health Sciences Center Department of Pathology, Shreveport, Louisiana, as authorized by the Caddo Parish Coroner. According to the pilot's autopsy report, his cause of death was blunt force injuries and his manner of death was accidental. The autopsy did not identify significant natural disease.

3.0 Toxicology

3.1 NMS Labs Toxicology Results

At the request of the Louisiana State University Health Sciences Center Department of Pathology, NMS Labs performed toxicological testing of postmortem specimens from the pilot.[1] Ethanol was detected at 0.014 g/dL in cardiac blood. Sertraline was detected at 41 ng/mL in cardiac blood, and the sertraline metabolite desmethylsertraline was detected at 70 ng/mL in cardiac blood. Amlodipine and caffeine were presumptively detected (detected by an initial test without a second test to confirm the result) in cardiac blood.

3.2 FAA Toxicology Results

The FAA Forensic Sciences Laboratory also performed toxicological testing of postmortem specimens from the pilot.[2] Sertraline was detected at 31 ng/mL, and its metabolite desmethylsertraline was detected at 53 ng/mL, in cardiac blood. Both sertraline and desmethylsertraline were also detected in urine. Bupropion was detected at 18 ng/mL, and its metabolite hydroxybupropion was detected at 128 ng/mL, in cardiac blood. Both bupropion and hydroxybupropion were also detected in urine. Quetiapine was detected at a low level in cardiac blood and was also detected in urine.[3] Gabapentin was detected at 719 ng/mL in cardiac blood and was also detected in urine. Pramipexole was detected in urine but was not detected in cardiac blood. Amlodipine was detected in cardiac blood and urine. Ethanol was not detected in cardiac blood.[4]

[1] NMS Labs tested cardiac blood per Test Code 8052B and urine per Test Code 8050U (report issued June 25, 2021). Additional information is available on the NMS Labs website at https://www.nmslabs.com/test-catalog.

[2] The FAA Forensic Sciences laboratory has the capability to test for around a thousand substances including toxins, prescription and over-the-counter medications, and illicit drugs.

[3] According to an e-mail from an FAA toxicologist, the quetiapine concentration in heart blood was below the lower limit of quantitation of the test, and significantly below typical therapeutic quetiapine concentrations.

[4] The FAA Forensic Sciences Laboratory uses an ethanol reporting threshold of 0.01 g/dL.

3.3 Descriptions of Detected Substances

Ethanol is the intoxicating alcohol in beer, wine, and liquor, and, if consumed, can impair judgment, psychomotor performance, cognition, and vigilance.[5,6,7] FAA regulation imposes strict limits on flying after consuming ethanol, including a prohibition on piloting a civil aircraft while having a blood ethanol level of 0.04 g/dL or greater.[8] Alcohol consumption is not the only possible source of ethanol in postmortem specimens. Ethanol can sometimes be produced by microbes in a person's body after death. Postmortem ethanol production is made more likely by extensive trauma.[9]

Sertraline is a prescription antidepressant medication of the selective serotonin reuptake inhibitor class. Desmethylsertraline is a metabolite of sertraline. Sertraline commonly is used to treat depression, and may also be used to treat a variety of other conditions.[10] Major depression can cause cognitive impairment, with potential adverse effects on reaction, memory, attention, problem solving, and task switching.[11] By contrast, sertraline has low potential to cause cognitive or psychomotor impairment, and may improve such impairment in individuals with major depression.[12,13,14] Sertraline's side effects may include dizziness and drowsiness, and

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[5] Federal Aviation Administration. Aeromedical factors. In: *Pilot's Handbook of Aeronautical Knowledge*. FAA H 8083 25C. Oklahoma City: United States Department of Transportation, Federal Aviation Administration, Airman Testing Standards Branch, AFS-630; 2023. https://www.faa.gov/regulations_policies/handbooks_manuals/aviation/phak/media/19_phak_ch17.pdf. Accessed August 8, 2023.

[6] Federal Aviation Administration. Fitness for flight. In: *Aeronautical Information Manual (AIM) Basic*. Washington, DC: United States Department of Transportation, Federal Aviation Administration, Mission Support Services, Policy Directorate, AJV−P; 2023. https://www.faa.gov/air_traffic/publications/atpubs/aim_html/chap8_section_1.html. Accessed August 8, 2023.

[7] Cook CCH. Alcohol and aviation. *Addiction*. 1997;92(5):539-555.

[8] 14 *Code of Federal Regulations* § 91.17.

[9] Kugelberg FC, Jones AW. Interpreting results of ethanol analysis in postmortem specimens: a review of the literature. *Forensic Sci Int*. 2007;165(1):10-29. doi:10.1016/j.forsciint.2006.05.004.

[10] National Institutes of Health National Library of Medicine. Zoloft. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fe9e8b7d-61ea-409d-84aa-3ebd79a046b5. Updated January 15, 2023. Accessed August 17, 2023.

[11] Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139(1):81–132. doi:10.1037/a0028727.

[12] Hindmarch I. The behavioural toxicity of the selective serotonin reuptake inhibitors. *Int Clin Psychopharmacol*. 1995;9 Suppl 4:13-17. doi:10.1097/00004850-199501004-00002.

[13] Paul MA, Gray G, Lange M. The impact of sertraline on psychomotor performance. *Aviat Space Environ Med*. 2002 Oct;73(10):964-70.

[14] Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. *Int J Neuropsychopharmacol*.

the drug typically carries a warning that users should not drive, operate heavy machinery, or do other dangerous activities until they know how the drug affects them.[10] A pilot on sertraline (not in combination with other psychiatric drugs) may be considered for FAA medical certification via special issuance only, because evaluation of the individual pilot's condition is required, including assessment of the pilot's cognitive function and response to medication.[15]

Bupropion, sometimes marketed as Wellbutrin, is another prescription medication that acts on the central nervous system (CNS). Bupropion can be used to treat depression and to help people quit smoking.[16,17] Hydroxybupropion is a metabolite of bupropion. Bupropion's mechanism of action and side-effect profile differs from other antidepressants; it does not typically cause sedation but may cause insomnia, and may increase susceptibility to seizures.[16,18] One small study of healthy subjects found no significant impact of sustained-release bupropion on psychomotor performance, including on tests intended to simulate flying performance.[19] In patients with major depression, bupropion may improve associated neurocognitive deficits.[20] Research on motor vehicle crash risk indicates that depression, antidepressants, or the combination of depression and antidepressants may present a safety hazard, but the independent contributions of antidepressants to that hazard generally are not well-defined.[21] Typically, bupropion carries a warning that any drug that acts on the CNS may impair users' ability to perform tasks requiring judgment or motor and cognitive skills, and that bupropion users should not drive or operate hazardous

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2015;19(2):pyv082. doi:10.1093/ijnp/pyv082.

[15] Federal Aviation Administration. Guide for aviation medical examiners: decision considerations - aerospace medical dispositions, item 47, psychiatric conditions - use of antidepressant medications. Federal Aviation Administration website. https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item47/amd/antidepressants. Updated June 28, 2023. Accessed August 17, 2023.

[16] National Institutes of Health National Library of Medicine. Wellbutrin XL. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a435da9d-f6e8-4ddc-897d-8cd2bf777b21. Updated March 4, 2022. Accessed August 18, 2023.

[17] National Institutes of Health National Library of Medicine. Wellbutrin SR. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cbc8c074-f080-4489-a5ae-207b5fadeba3. Updated December 6, 2022. Accessed August 18, 2023.

[18] Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry*. 2004;6(4):159-166. doi:10.4088/pcc.v06n0403.

[19] Paul MA, Gray G, Kenny G, Lange M. The impact of bupropion on psychomotor performance. *Aviat Space Environ Med*. 2002;73(11):1094-1099.

[20] Gualtieri CT, Johnson LG. Bupropion normalizes cognitive performance in patients with depression. *MedGenMed*. 2007;9(1):22.

[21] Hill LL, Lauzon VL, Winbrock EL, Li G, Chihuri S, Lee KC. Depression, antidepressants and driving safety. *Inj Epidemiol*. 2017;4(1):10. doi:10.1186/s40621-017-0107-x.

machinery until they are reasonably certain that the drug does not adversely affect their performance.[16,17] According to the FAA medical case review for this crash, bupropion was considered disqualifying for pilot medical certification. In May 2023, the FAA added extended-release and sustained-release (but not immediate-release) formulations of bupropion to the list of antidepressants that (not used in combination with other psychiatric drugs) may be considered for FAA medical certification via special issuance.[15]

Quetiapine, sometimes marketed as Seroquel, is a prescription antipsychotic medication. In the United States, quetiapine is approved by the Food and Drug Administration (FDA) for treating schizophrenia. Quetiapine is also FDA-approved for treating acute episodes of mania and depression in bipolar disorder, and as part of chronic multi-drug treatment of bipolar disorder. Additionally, quetiapine is approved as part of multi-drug treatment of major depressive disorder. Quetiapine is regularly prescribed for off-label (non-FDA-approved) uses, including in low doses for treatment of insomnia without underlying psychiatric illness. Some other possible off-label uses include chronic single-drug treatment of bipolar disorder, as well as treatment of post-traumatic stress disorder and anxiety.[22 - 28] Quetiapine may also be

[22] National Institutes of Health National Library of Medicine. Seroquel. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0584dda8-bc3c-48fe-1a90-79608f78e8a0. Updated January 27, 2022. Accessed August 18, 2023.

[23] Stovall J. Bipolar mania and hypomania in adults: choosing pharmacotherapy. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/bipolar-mania-and-hypomania-in-adults-choosing-pharmacotherapy. Updated July 29, 2022. Accessed August 18, 2023.

[24] Shelton RC, Bobo WV. Bipolar major depression in adults: choosing treatment. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/bipolar-major-depression-in-adults-choosing-treatment. Updated May 19, 2022. Accessed August 18, 2023.

[25] Post RM. Bipolar disorder in adults: choosing maintenance treatment. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/bipolar-disorder-in-adults-choosing-maintenance-treatment. Updated April 19, 2023. Accessed August 18, 2023.

[26] Thase ME. Quetiapine monotherapy for bipolar depression. *Neuropsychiatr Dis Treat*. 2008;4(1):11-21.

[27] Neubauer DN. Pharmacotherapy for insomnia in adults. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/pharmacotherapy-for-insomnia-in-adults. Updated May 24, 2023. Accessed August 18, 2023.

[28] Modesto-Lowe V, Harabasz AK, Walker SA. Quetiapine for primary insomnia: consider the risks. *Cleve Clin J Med*. 2021;88(5):286-294. doi:10.3949/ccjm.88a.20031.

misused or abused, often in combination with other recreational substances.[28 – 31] Quetiapine commonly causes drowsiness, especially in the initial days after starting a treatment regimen; users may develop tolerance to this effect over time. Quetiapine typically carries a warning that it has the potential to impair judgment, thinking, and motor skills, and that users should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, until they are reasonably certain that the drug does not affect them adversely.[22,32] The FAA considers quetiapine to be a "Do Not Issue/Do Not Fly" medication.[33] According to the FAA medical case review for this accident, quetiapine is unacceptable for FAA medical certification.

Gabapentin is a prescription medication that can be used to treat nerve pain, certain types of seizures, restless legs syndrome, and other conditions. Gabapentin may cause sedation and dizziness and can impair coordination and performance of tasks such as driving and operating heavy machinery. The drug typically carries a warning that users may not be able to accurately assess how sleepy or impaired it makes them, and that they should not drive or operate complex machinery until they have gained enough experience to determine whether the drug impairs their ability to do so.[34,35] The FAA considers gabapentin to be a "Do Not Issue/Do Not Fly" medication.[33] According to the FAA medical case review for this accident, regular use of gabapentin for any reason is disqualifying for pilot medical certification.

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[29] Mattson ME, Albright VA, Yoon J, Council CL. Emergency department visits involving misuse and abuse of the antipsychotic quetiapine: results from the Drug Abuse Warning Network (DAWN). *Subst Abuse*. 2015;9:39-46. doi:10.4137/SART.S22233.

[30] Kim S, Lee G, Kim E, Jung H, Chang J. Quetiapine misuse and abuse: is it an atypical paradigm of drug seeking behavior? *J Res Pharm Pract*. 2017;6(1):12-15. doi:10.4103/2279-042X.200987.

[31] Klein L, Bangh S, Cole JB. Intentional recreational abuse of quetiapine compared to other second-generation antipsychotics. *West J Emerg Med*. 2017;18(2):243-250. doi:10.5811/westjem.2016.10.32322.

[32] Jibson MD. Second-generation antipsychotic medications: pharmacology, administration, and side effects. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects. Updated May 9, 2023. Accessed August 18, 2023.

[33] Federal Aviation Administration. Guide for aviation medical examiners: pharmaceuticals (therapeutic medications) do not issue - do not fly. Federal Aviation Administration website. https://www.faa.gov/ame_guide/pharm/dni_dnf. Updated July 10, 2023. Accessed August 18, 2023.

[34] National Institutes of Health National Library of Medicine. Neurontin. DailyMed. https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=ee9ad9ed-6d9f-4ee1-9d7f-cfad438df388. Updated July 12, 2022. Accessed August 18, 2023.

[35] Peterson BL. Prevalence of gabapentin in impaired driving cases in Washington State in 2003–2007. *J Anal Toxicol*. 2009;33(8):545-549. doi:10.1093/jat/33.8.545.

Pramipexole is a prescription medication that may be used to treat Parkinson's disease, a neurological condition that may impair motor and cognitive function.[36,37] Pramipexole also may be used to treat restless legs syndrome, a neurological condition that causes a strong urge to move the legs, potentially interfering with sleep.[38,39] Pramipexole frequently causes sedation and can cause episodes where users fall asleep without warning during daily activities. The drug typically carries a warning that users should not drive or engage in other potentially dangerous activities until they have gained sufficient experience with the drug to gauge whether or not it affects their mental and/or motor performance adversely.[36,38] The FAA considers pramipexole to be a "Do Not Issue/Do Not Fly" medication.[33] According to the FAA medical case review for this accident, pramipexole is unacceptable for pilot medical certification.

Amlodipine is a prescription medication that can be used to treat high blood pressure and certain types of coronary artery disease.[40] Caffeine is a central nervous system stimulant that is commonly ingested, including in coffee, tea, soft drinks, and chocolate, and is also an ingredient in certain anti-drowsiness medications and headache medications.[41,42] Amlodipine and caffeine are not generally considered impairing.

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[36] National Institutes of Health National Library of Medicine. Mirapex ER. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2902ed1-cfeb-4815-adc3-129c577917a1. Updated May 1, 2018. Accessed August 18, 2023.

[37] National Institutes of Health National Institute on Aging. Parkinson's disease: causes, symptoms, and treatments. Health Topics A-Z. https://www.nia.nih.gov/health/parkinsons-disease. Updated April 14, 2022. Accessed August 18, 2023.

[38] National Institutes of Health National Library of Medicine. Pramipexole dihydrochloride. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fe7106d-4bf6-4794-87cb-8df616994c41. Updated March 7, 2023. Accessed August 18, 2023.

[39] National Institutes of Health National Institute of Neurological Disorders and Stroke. Restless legs syndrome. Health Information. https://www.ninds.nih.gov/health-information/disorders/restless-legs-syndrome. Updated August 1, 2023. Accessed August 18, 2023.

[40] National Institutes of Health National Library of Medicine. Norvasc. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abd6a2ca-40c2-485c-bc53-db1c652505ed. Updated April 4, 2022. Accessed August 18, 2023.

[41] National Institutes of Health National Library of Medicine. NoDoz Alertness Aid. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e700e809-29b5-799e-e053-2a95a90a235c. Updated October 11, 2022. Accessed August 18, 2023.

[42] National Institutes of Health National Library of Medicine. Fioricet. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c018be7d-f7b8-45e2-97b8-8e7a71740657. Updated January 1, 2021. Accessed August 18, 2023.

E. SUMMARY OF MEDICAL FACTS

The 73-year-old male pilot's last aviation medical examination was on April 24, 2020. At that time, he reported no medication use and no active medical conditions. He was issued a third-class medical certificate limited by a requirement to have available glasses for near vision.

According to the pilot's autopsy report, his cause of death was blunt force injuries and his manner of death was accidental. The autopsy did not identify significant natural disease.

Postmortem specimens from the pilot underwent toxicological testing by NMS Labs and the FAA Forensic Sciences Laboratory. NMS Labs testing detected ethanol at 0.014 g/dL, sertraline at 41 ng/mL, and desmethylsertraline at 70 ng/mL, in cardiac blood; amlodipine and caffeine were presumptively detected in cardiac blood. In cardiac blood, the FAA Forensic Sciences Laboratory detected sertraline at 31 ng/mL, desmethylsertraline at 53 ng/mL, bupropion at 18 ng/mL, hydroxybupropion at 128 ng/mL, quetiapine at a low level, gabapentin at 719 ng/mL, and amlodipine; each of these substances was also detected in urine, while pramipexole was detected in urine but not in cardiac blood. FAA testing of cardiac blood did not detect ethanol.

Submitted by:

Turan Kayagil, MD, FACEP
Medical Officer