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Pilots using selective serotonin reuptake inhibitors compared to other fatally injured pilots

Paul Rogers[a,*], Christy Hileman[a], Guillermo Salazar[a], Kacey Cliburn[a], Lawrence Paskoff[a], William Hathaway[a], Kevin Gildea[a], Victor Hugo Tejera Villalaz[b]

[a] Federal Aviation Administration, Civil Aerospace Medical Institute, United States
[b] National University of Columbia, Colombia

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ABSTRACT

Selective Serotonin Reuptake Inhibitors (SSRI) were a disqualifying medication for U.S. civil pilots before April 5, 2010. After this date, a Federal Aviation Administration policy was created that allowed airmen, on select SSRIs, a pathway to hold a valid medical certificate. The purpose of this study was to provide a detailed look at SSRIs in the U.S. pilot population since the inception of this new policy. We examined the toxicology results from fatally injured airmen in addition to outcomes concerning pilots who are participating in the program. This study examined data from the Civil Aerospace Medical Institute's Bioaeronautical Sciences Research Laboratory in conjunction with the Medical Analysis Tracking Registry and the Document Imaging and Workflow System. A count-based regression model quantified the relationships between positive SSRI findings with additional factors of interest. These factors included pilot rating, ethanol, and first generation antihistamines. There were 1484 fatally injured airmen over the six year study period, of which 44-tested positive for an SSRI. First-generation antihistamines were statistically associated with positive findings of SSRIs.

1. Introduction

The Centers for Disease Control and Prevention (CDC) reported that antidepressant use in the United States increased nearly 400% between periods spanning 1988–1994 and 2005–2008 (Pratt et al., 2011). Overall, they were the third most common prescription medication in use from 2005 to 2008 by Americans of all ages, and the most frequently used drug in the 18–44 age group. It was reported from 2005 to 2008 that 11% of all Americans over the age of 12 were taking an antidepressant. In the 2012 CDC National Ambulatory Medical Survey, out of the 20 categories to which 3583 physicians responded, antidepressants and anxiolytics/sedatives/hypnotics were the third and fourth most prescribed medications (CDC-NCHS, 2012). The increasing prevalence of antidepressant use in the U.S. general population raises a number of questions concerning the U.S. pilot population. These questions are of interest to policy makers, regulators, and the flying public.

Before April 2010, the use of antidepressants was considered disqualifying for pilots seeking a Federal Aviation Administration (FAA) airman medical certificate. The disqualification was due to the medication and/or the underlying medical condition being treated. The FAA conducted an extensive review of the experiences of Transport Canada and the Civil Aviation Safety Authority in Australia assessing the risks and benefits of antidepressant usage in civil aviation (Ross et al., 2007; Federal Aviation Administration (US), 2010; Jones and Ireland, 2004). Starting April 5, 2010, the FAA permitted an Authorization for Special Issuance of a Medical Certificate (Authorization) for airmen on selected Selective Serotonin Reuptake Inhibitors (SSRI), a group of antidepressants better tolerated by patients than older tricyclic (TCA) drugs (Federal Aviation Administration, 2017). The selected SSRIs were fluoxetine (Prozac®), sertraline (Zoloft®), citalopram (Celexa®) and escitalopram (Lexapro®) (Berry, 2010). Allowing a Special Issuance for selective SSRIs signified a shift in long-standing FAA policy regarding antidepressants and deserves closer study.

In order to qualify for this Authorization an airman may only have had one of the following diagnoses: 1. major depressive disorder that was mild to moderate and could have been single or recurrent; 2. dysthymic disorder; 3. adjustment disorder; or 4. any non-depression related condition for which an SSRI would be needed. Furthermore, the condition needed to have been stable for a minimum of six continuous months prior to the application for an Authorization and on an established dose of medication. Finally, the applicant must never have had

* Corresponding author.
E-mail addresses: paul.rogers@faa.gov (P. Rogers), christy.hileman@faa.gov (C. Hileman), G.J.Salazar-MD@faa.gov (G. Salazar), kacey.cliburn@faa.gov (K. Cliburn), lawrence.paskoff@faa.gov (L. Paskoff), william.hathaway@faa.gov (W. Hathaway), kevin.gildea@faa.gov (K. Gildea), vhtejerav@unal.edu.co (V.H. Tejera Villalaz).

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any of the following: psychosis, suicidal ideation, electro-convulsive therapy, treatment with multiple SSRIs concurrently, or multi-agent drug protocol use (i.e., prior use of other psychiatric medications in conjunction with SSRIs). The airman would engage a specially designated Human Intervention Motivation Study (HIMS) Aviation Medical Examiner (AME) to assist in submitting all required information, and if all these criteria were met the Federal Air Surgeon would consider the airman for an Authorization for Special Issuance of a medical certificate for continued use of the SSRI (Berry, 2010; Federal Aviation Administration, 2017).

SSRIs were frequently found in conjunction with other medications during toxicological testing of biological samples from aircraft crash victims. A previous study covering the period 1990–2001 of 61 fatally injured airmen who tested positive for an SSRI, found that 39 of the 61 had other drugs present (Akin and Chaturvedi, 2003). Diphenhydramine, a first-generation antihistamine, was the most common drug found in fatally injured pilots (Canfield et al., 2011). Ethanol was also a widely used drug, frequently discovered in the samples taken from fatally injured pilots; one study reported finding ethanol in 7% of this group (Chaturvedi et al., 2016). Alcohol and first-generation antihistamines are considered impairing substances, which may work synergistically with the side effects of SSRIs. Both alcohol and antihistamines are central nervous system depressants with adverse effects on neuronal activity resulting in sedation and cognitive impairment (Dry et al., 2012; Fox et al., 2014; Woehrling et al., 2015). The use of diphenhydramine together with fluoxetine, sertraline, escitalopram, or citalopram may increase side effects such as dizziness, drowsiness, and difficulty concentrating. Also, there was evidence that alcohol and SSRIs, in combination, lead to unexpected behaviors (Menkes and Herxheimer, 2014).

The aim of this study was to provide a statistical and descriptive analysis to identify factors and trends associated with the use of SSRIs within the fatally injured civil pilot population. Further, this study was conducted to determine if it is possible to quantify and describe the relationship of SSRI use with other crash factors within this population. These other factors included pilot instrument rating, ethanol, and first-generation antihistamines. This information will be of use in the formulation of recommendations concerning SSRIs within the aviation community.

2. Methods

In this project, the population of interest was fatally injured aviators; this group was selected as toxicology and autopsy information were readily available and required to confirm the presence or absence of specific drugs or medications. The FAA performs toxicology and collects autopsy information on all pilots fatally injured in general aviation crashes. In addition, this research relied upon the Medical Analysis Tracking (MANTRA) Registry system maintained by the Autopsy Program Team located at the Civil Aerospace Medical Institute (CAMI). MANTRA is a nexus for varied sources of information on fatal aerospace incidents. These sources included the National Transportation Safety Board (NTSB), Document Imaging Workflow System, Airmen Registry, toxicology results, and the autopsy reports submitted from medicolegal death investigations. The study timeframe spanned from October 1, 2008 through September 30, 2014 corresponding to the 2009–2014 government fiscal years.

The SSRIs examined in this research included the following: SSRIs allowable under the FAA SSRI policy (citalopram, escitalopram, fluoxetine, and sertraline) and other non-approved SSRIs (fluvoxamine, paroxetine, vilazodone, indalpine, and zimelidine). We queried MANTRA for findings involving any of the listed SSRIs. Once matched, we pulled the entire case for a more detailed examination.

In order to quantify the relationships of the data in the various systems we used regression techniques. Typically, analyzing the occurrence of adverse events in the aviation environment involves the modeling of rare events. Therefore, a count-based Poisson regression model was employed to explore the relationship of SSRIs with factors related to the aviators' instrument rating, antihistamines, and ethanol. The Poisson distribution can be defined in terms of a single parameter (λ) as:

$$f(k;\lambda) = \frac{e^{-\lambda}\lambda^{k}}{k!},\ k = 0,\ 1,\ 2,\ldots\ldots \tag{1.0}$$

Where λ typically represents the rate, in terms of event occurrence, and k is the number of these events. The event (k) is the discovery of a SSRI in the toxicology of a fatally injured airman. Eq. (2.0) describes the dependent variable in terms of the log counts of fatally injured accident airmen:

$$\ln[\text{Count}(SSRI\ Airmen)] = \beta_0 + \beta_1{*}(Instrument\ Rating) + \beta_2{*}(Ethanol) + \beta_3{*}(Antihistamine) + \beta_4{*}(Antihistamine{*}Ethanol) + \ln(offset)$$

Another predictor in the Poisson model, the *offset* or exposure, does not have a regression coefficient to be estimated. The offset represents the denominator, or total number of airmen, in a particular category or *covariate pattern*. We needed to include this offset to calculate the results in terms of Incident Rate Ratios (IRR) within the regression model.

One of the fundamental assumptions in Poisson regression is that the mean and variance are equal: $\lambda = \mu$ was a necessary condition for producing valid standard errors for the regression coefficients. Slight departures from this assumption can be compensated for with the use of a dispersion parameter used to scale the standard errors (Hilbe, 2014). In this study, the dispersion parameter was set equal to Pearson's Chi-Square statistic divided by its degrees of freedom to adjust the model's standard errors.

The model produced results in terms of IRRs in units of Person-Years for individual rates. The statistically insignificant variables were removed in a backward elimination process assessing interaction terms before their main effects. All analyses were performed in Statistical Analysis Software (SAS) version 9.4. The level of significance for all tests was set at $\alpha \leq 0.05$.

2.1. Variable categorization and classification

2.1.1. SSRI

The count of *SSRI* cases was the outcome variable of interest. The total number of fatalities was represented by the *offset* in the model for each covariate pattern.

2.1.2. Instrument

The variable *Instrument* indicated if the airmen held an instrument rating. An instrument rating is the additional training required to fly under instrument flight rules and was intended to be a surrogate variable for both proficiency and as an experience measure. It was created as a binary variable, with a one indicating that the airman held an instrument rating and a zero otherwise. The counts of this variable were then summed for each category.

2.1.3. Ethanol

Ethanol is an impairing drug frequently found in the fatally injured airmen population. However, ethanol may also be produced post-mortem by bacteria; therefore, it was extremely important to determine the source of the ethanol. The presence of certain substances, such as n-propanol, n-butanol and serotonin metabolites, might suggest post-mortem production, but this must be considered with care. In a study by Chaturvedi et al. spanning years 1989–2013, 85 of the 1169 cases tested positive for ethanol (Chaturvedi et al., 2016). Of these 85 cases that tested positive for ethanol, six (7.1%) of these findings were deemed to have been due to post-mortem production of ethanol. This finding provided a rough estimate of the rate at which samples were affected by the post-mortem production of ethanol. If the proportion of