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Bipolar Disorder in Aviation Medicine

Alpo Vuorio; Tanja Laukkala; Pooshan Navathe; Bruce Budowle; Robert Bor; Antti Sajantila

- BACKGROUND:** One of the most difficult challenges in aviation medicine is to diagnose, as early as possible, pilots with psychiatric disorders that may impair pilot performance and increase the risk of incidents and accidents. This diagnosis applies particularly to bipolar disorder (BD), where return to flying duty is not an option in the majority of cases. BD is a long-term mental disorder presenting remittent depressive, hypomanic, manic, or mixed episodes between low symptomatic or asymptomatic intermediate periods. Onset in most cases is in late teen or early adult years. Suicidal intentions and suicide risk are significantly elevated in individuals with BD compared to the general population.
- METHODS:** A systematic literature search was performed of BD and aviation accidents and the National Transportation Safety Board database of fatal general aviation accidents was searched. One case report and two database reports of interest from 1994 to 2014 were identified.
- RESULTS:** The findings set a minimum frequency of BD in general aviation fatalities to be approximately 2 out of 8648 (0.023%) in the United States.
- DISCUSSION:** The reported incidence may underestimate the real number of BD cases for several reasons, including the fact that the medical history of pilots is not always available or is sometimes not the primary interest of a safety investigation. This study suggests that the demarcation of psychiatric disorder related to fitness to fly is an important step in safety.
- KEYWORDS:** bipolar disorder, accident, aviation, psychiatry.

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One of the most difficult challenges in aviation medicine is the identification and diagnosis of pilots with specific psychiatric disorders that may adversely affect pilots' performance.^{1,2,11,12} Early diagnosis allows, on a case-by-case basis, treatment of the disorder with the best possible options and outcomes, and the opportunity to determine, if or when, a pilot may resume flying after adequate treatment and monitoring. In some countries treated, stable and monitored depression in a pilot may allow for flying in the absence of specific excluding criteria.³⁵ There are, however, certain long-term psychiatric conditions, such as bipolar disorder (BD), where commencing flight training or return to flying duty is not an option among pilots, whether involved in general or commercial aviation, seeking a medical license from any of the major crew licensing authorities. It is very rare that a pilot will receive medical certification with a known status of BD, since the consequences that may follow can be unpredictable and threaten flight safety. Pilots may be unwilling to report any significant psychiatric condition which may compromise their medical status or indeed be unaware that their condition prevents them from holding valid medical certification.¹⁷ The

recent pilot suicide murder crash on 24 March 2015 of Germanwings Flight 9525 while flying over the French Alps emphasizes the importance of aeromedical assessment among pilots who suffer from psychiatric disorders, good communication between health care professionals, and the difficulty of establishing a clear clinical diagnosis of the condition post-mortem.^{6,37} BD, its effects, and the challenges related to pilots involved in civil aviation who may have BD are discussed in this paper.

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Bipolar Disorder in the Wider Population

BD is a long-term mental disorder presenting remittent depressive, hypomanic, manic, or mixed episodes between low symptomatic or asymptomatic intermediate periods. BD often starts in late teen or early adult years. Among over 61,000 adults in 11 countries in the Americas, Europe, and Asia, aggregate lifetime prevalence was 0.6% for bipolar type I disorder, 0.4% for bipolar type II disorder, 1.4% for subthreshold BD, and 2.4% for bipolar spectrum disorders.²³ According to the DSM-5,¹⁰ the bipolar type I disorder criteria (recurring manic episodes) represent the modern understanding of the classic manic-depressive disorder and bipolar type II disorder (hypomanic episodes and major depressive episodes) is no longer thought to be a “milder” condition than bipolar type I disorder. This distinction is largely because of the amount of time individuals with this condition spend in depression and because of accompanying serious impairment in work and social behavior.¹⁰ In addition, DSM-5 diagnostic classification recognizes cyclothymic disorder, substance/medication-induced BD, and related disorders.

BD in the general population is often comorbid with other disorders such as anxiety disorders, personality disorders, attention deficit hyperactivity disorder, and substance misuse.³² Depressive symptoms are similar in bipolar and unipolar depression, but symptom-rating scales, such as the Mood Disorder Questionnaire,³⁸ are useful in assessing elevated mood. Suicidal intentions and suicide risk, which are elevated in individuals with BD as compared to the general population, can be evaluated, e.g., with the Columbia Suicide Severity Rating Scale (<http://cssrs.columbia.edu/>). Even in psychiatric evaluation or care, BD is often recognized only after a substantial period of time.²⁰

Treatment of BD focuses on drug treatment of acute manic and depressive phases, and prevention of the recurrence of episodes in the long term using medication sometimes combined with structured psychotherapy. Pharmacological interventions usually include mood stabilizers such as lithium and some anti-epileptics and antipsychotics. During mania, hypomania, or major depressive episodes, other psychotropic medications are combined according to the phase of disorder (e.g., antipsychotics olanzapine, risperidone, and haloperidol for mania and, e.g., quetiapine or antidepressants combined with mood stabilizers for the depressive phase). In the long term, lithium still has the best response in preventing relapses.^{15,24}

There has been recent emphasis in the field of biomarker tests in clinical practice for their use and application for detecting certain mental disorders.⁷ From the clinical perspective, a major challenge is the delay between onset of the mental disorder and initiation of effective medication. This delay is especially relevant for BD. Informative biomarker testing may help shorten this delay, or even prevent treatment failures. Current diagnostic criteria are a description of how mental disorders are expressed and can be recognized.¹⁰ This phenotype-based diagnostic system is not able to differentiate whether bipolar patients have different gene and protein level alterations, but rather combines patients with the same type of symptoms. The study by Fabbri and Serreti¹³ showed that it may be feasible to

link genetics to long-term treatment outcomes. This finding might offer new possibilities in aeromedical decision-making. Mathieu *et al.*²¹ showed that it is possible to identify interaction of certain candidate genes and this phenotype. Furthermore, a recent study by the International Consortium on Lithium Genetics (www.ConLiGen.org) suggested that genetic testing may provide insight to sort out patients who are responders or nonresponders to lithium.¹⁶

Bipolar Disorder in the Pilot Population

Since BP is a relatively prevalent condition with a risk of recurrence even with drug treatment, there is a need to estimate the number of general aviation fatalities involving pilots with BD and to compare medical requirements concerning BD by aviation authorities in different countries. Postmortem aviation forensic pathology is an obligatory part of aircraft accident investigation based on Annex 13, which guides aircraft accident investigations.¹⁸ The aim is to help to establish the cause, manner, and circumstances of the death, and help to understand whether toxicological findings were related to human performance of the pilot.⁹ It can be postulated that aviation pathology is a clear example of complexity regarding rendering forensic pathological conclusions. Usually the human body is substantially destroyed, toxicological analysis is difficult to interpret, available medical history is incomplete, and drug-related human performance alterations are difficult to determine. This complexity should be appreciated when seeking to analyze relevant impact of medical issues with a case. In fact, Jones¹⁹ has discussed very topically this issue in his communication related to complexity in forensic pathology. It can be envisioned that incorporation of complex thinking is important in understanding forensic aviation pathology.

In the case of a pilot with BD, toxicological analytic methods attempt to clarify what impact, if any, there is of drugs or other possible foreign substances in toxicological findings in addition to BD itself. If the medical history of the deceased pilot is incomplete, which is often the case, the unexpected presence of drugs in toxicological analytics may indicate a need to re-evaluate the medical history to determine the underlying medical disease or condition which led to the drug use. In very rare cases, a deceased pilot is not found or the body is so badly damaged that it is impossible to take toxicological samples.

If a fatal aircraft accident occurs in the United States, all toxicological analyses are carried out by the FAA laboratory.⁹ This approach allows an analysis of the same components in each case and produces comparative postmortem toxicological data for later analyses. The FAA laboratory operates also as the reference laboratory, allowing quality assurance and quality control for other forensic laboratories working with forensic samples.⁸

The samples are analyzed without any knowledge of the medical history of the deceased pilot.⁹ This gap further emphasizes the importance of accident investigators' efforts to access pilots' medical histories. Unfortunately, gathering a medical history is very laborious. In many cases, conclusions by an accident investigator are reached on toxicological analysis alone. In the two cases discussed here with potential BD medication

present in the postmortem blood, it would have been mandatory to reach out for an indication of the medication. Investigators also may need to carry out a psychological autopsy and try to go back many years in the medical history with the help of interviews and any records available of the pilot's history.³⁶

From a toxicological analysis point of view, the postmortem drug redistribution is a clear challenge.^{22,29} In the study carried by Staeheli *et al.*,²⁹ venlafaxine, flupentixol, paroxetine, and lorazepam generally showed a decline by over 30% in the admission to autopsy and after 24 h. This finding demonstrates clearly the challenges to analyzing postmortem samples sometimes taken after a substantial delay.

Sen *et al.*²⁸ reported that there were 61 fatal accidents in the United States in which postmortem antidepressant residues were detected in deceased pilots. In only 11 of the 61 cases (18%) were medical histories of pilots available. In 1 of the 11 cases (9.1%, 1.6% of all cases), medical files documented fluoxetine treatment due to BD. Obviously, postmortem toxicological data should be cautiously interpreted in order to make any definite conclusion of pilots' diseases without access to their medical records. Medication used for BD is also used to treat other neurological (such as some types of epilepsy) and psychiatric disorders. For example, fluoxetine, which was found in both of the cases described in this study, is more often used to treat depression than BD and, generally, fluoxetine treatment in BD is not supported by clinical guidelines.²⁴

The Transportation Safety Board of Canada has published an accident report related to a fatal aircraft accident and pilots with BD.³⁰ The report describes an accident of a Piper J4A aircraft, which banked steeply straight after the initial takeoff. The postmortem toxicological analysis revealed lithium in the pilot's blood sample. There was no information on regular medication in the pilot's aeromedical files. Lithium is approved for primary use for treatment of BD, especially for the manic phases and as a maintenance drug. Lithium treatment is associated with a decrease in all-cause and suicide mortality in a large nationwide high-risk BD cohort.³¹ Since lithium also has some off-label use, it is difficult to draw a conclusion as to basis of the treatment. However, it is known that lithium may cause many adverse effects, including visual problems as well as vertigo. No causal connection was drawn between the health of the pilot and the accident. This report illustrates the inherent difficulties in drawing conclusions as to whether a medication that is known to impair performance is actually a causal link with an accident. In such situations, it is recommended to carry out a psychological autopsy in addition to a physical autopsy and toxicological analyses.³⁶ In a psychological autopsy, a pilot's medical and social history is collected several months or even years preceding the accident, and as recommended by the International Civil Aviation Organization's Clinical Practice Guidelines Annex 1318, is not limited to a couple of days preceding the event.

Aeromedical Examination Regarding Mental Disorders

Psychiatric disorders among student pilots as well as licensed pilots are among the top five reasons for loss of medical license.⁴

There are several challenges to assessing and diagnosing mental health problems among pilots. Most would be unaware of the specific mental health exclusions and arguably a proportion would be unaware that they are suffering from an excluding or serious mental health problem. It is common knowledge among AMEs and aviation regulators that social stigma and a fear of losing one's livelihood through the loss of one's medical certification mitigate against openness about medical and mental health problems among pilots when being assessed by their AME.⁵ Arguably, some mental health conditions, such as BD or significant alcohol misuse, among others, can affect higher level cognitive functioning, leading to nondisclosure due to lack of insight and reduced self-awareness. AMEs may require further training in carrying out mental health assessments in the context of their time-pressured routine annual pilot medicals⁵ and in accessing collateral information about the pilot, including the pilot's general medical records, feedback from other family members, school records, etc. Mental health assessments that rely exclusively on the pilot's mental state in the AME examination and the pilot's self-reported history may be inadequate or insufficiently robust to be accurate. It is also important that pilots are better educated about the potential deleterious effects of some serious mental health conditions on pilot performance and safety, even when these are neither present nor florid.

A systematic literature search was performed of BD and aviation accidents that may have occurred over the last three decades and identified known cases of aviation fatalities in the United States in which pilots were diagnosed with BD. The possibilities for investigating these accidents are discussed, particularly with the aim of identifying diagnostic signs of BD, e.g., in medical records or postmortem toxicology, and potential methods of prevention.

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METHODS

A PubMed search was carried out to identify publications related to BD and aviation safety from 1982 to October 2015. The search terms were "aviation" OR "aviation accident" OR "aircraft accident" AND "bipolar disorder." This search revealed five articles, but they were not related to pilots and BD. Only one relevant case report related to a pilot with BD and a fatal accident was found when analyzing aviation websites of aviation authorities from the United States, Canada, Australia, and Europe. To identify fatal accidents in general aviation (including in addition airplanes and helicopters as well as balloons and gliders) in the United States between the years 1994 to 2014, the National Transportation Safety Board (NTSB) database was analyzed.²⁵ The interactive search machine was used, allowing input of certain preconditions. Those fatal general aviation accidents, found with a search term "bipolar disorder," were analyzed further (search date 2 March 2016). Additionally, the medical requirements of different aviation authorities from the United States,¹⁴ Australia,³ Canada,³⁴ and Europe¹² were compared.

RESULTS

In a PubMed search, no relevant articles related to pilots with BD and fatal accidents in aviation were found. Only one related case study was found at one aviation authority website.³⁰ The comparison of aviation authorities' policies showed that none of the aviation authorities (Table I; European Aviation Safety Agent,¹² United States Federal Aviation Administration,¹⁴ Australian Civil Aviation Safety Authority,³ and Transport Canada³⁴) allowed individuals with BD to pilot aircraft.

The NTSB database search for fatal general aviation accidents related to BD yielded two reports from 1994 to 2014 in the United States with probable pilot BD. The first was with five victims, where pilot BD was diagnosed by a psychiatrist, and the other was a glider accident with a pilot who had a self-reported history of BD and insomnia. Postmortem toxicology showed the use of fluoxetine and mirtazapine, no ethanol in the first case and fluoxetine, norfluoxetine, and hydrocodone were observed in the second case without mention of ethanol. The National Transportation Safety Board determined the probable cause(s) of the accidents as follows: the pilot initiating flight into known adverse weather conditions without proper certification. Factors were the meteorological conditions that existed—low ceiling, low visibility, and falling snow—and his use of contraindicated drugs and, in the second accident, the pilot's failure to maintain obstacle clearance, resulting in an in-flight collision with a static wire and an uncontrolled descent and collision with the ground. A factor in the accident was the pilot's impairment resulting from the use of unapproved medication.

There were six additional reports in the NTSB database search in which psychiatric symptoms were described, varying from addictions to anxiety, from depressive to psychotic symptoms, or in which postmortem analysis revealed a use of medication or other psychotropic substances. However, the data were insufficient to determine whether BD had been considered as a possible diagnosis.

DISCUSSION

Fatal aviation accidents in general aviation with pilots suffering from BD in the United States between the years 1994 and 2014 were reviewed in this study. Nonfatal accidents were not included in this study, which excluded one potential BD accident. Background medical data were often insufficient, limiting the evaluation of potential cases. Two deceased pilots had diagnosable BD, one self-reported and one diagnosed by a

psychiatrist. These findings, based on a NTSB database search for fatal general aviation accidents, set a minimum frequency of BD in general aviation pilot fatalities to be approximately 2 out of 8648 (0.023%) in the United States. This value may underestimate the real number of BD cases for several reasons, including the fact that the complete medical history of pilots is not always available or is sometimes not the primary interest of the safety investigation.

Aeromedical decision making regarding bipolar disorder without symptoms may theoretically find neither risk nor danger to a pilot. However, the nature of BD is such that both depressive and manic states can significantly alter cognitions and behaviors, and there is an increased risk of suicide in the affected individual. Furthermore, the pilot suffering with BD may lack insight and exercise poor judgment when affected by the highs and lows that characterize this condition. This effect in turn can impair self-regulation and therefore the pilot may not seek professional help, take his/her medication regularly and as prescribed, or ground him/herself during these episodes. Specifically, the symptoms of instability, unpredictable mood swings, hypomania, increased risk-taking, grandiosity, sleep disruption, racing thoughts, disrupted communication patterns, agitation, withdrawal, anhedonia, indecisiveness and inability to make decisions, among many others, would all likely degrade mental focus and reaction times and at a minimum pose a risk to air safety.²⁷

Depressive episodes of BD do not differ from depressive episodes of unipolar major depression. Thus, it is essential that clinicians ask about the earlier history of elevated mood symptoms when they treat depression. Even in psychiatric settings, BDs are recognized only after a substantial time period.²⁰ Diagnosis of BD in the aviation medicine setting also may be problematic as the person: 1) has an interest in nondisclosure; 2) may lack insight into their condition; 3) may present to the AME in a stable and symptom-free state, making diagnosis more difficult; and 4) cyclothymic episodes may mimic aspects/patterns of BD, rendering accurate assessment and diagnosis problematic. As BD is essentially an excluding condition, diagnosis is in some cases only made post hoc, or not even at that point, following an incident or accident. Evidence and testimony at this stage are less reliable and accurate than a patient assessment.

A major challenge is to determine if pilots can be allowed to fly with BD and symptom-based varied medication. BD is currently a disqualifying factor for general and commercial aviation, and thus pilot candidates may not voluntarily report their disease status for fear of being prevented from undertaking pilot training. The special group will be in future those pilots

Table I. Different Aviation Authorities and Fitness to Fly with Bipolar Disorder.

AVIATION AUTHORITY	EASA	TRANSPORT CANADA	FAA	CASA
BD & Aviation Arguments	Disqualifying*	Disqualifying*	Disqualifying* Judgment & functioning risk in mania	Disqualifying* Suicide in 10–15% of cases. If mania once, 90% have it again & MD

EASA = European Aviation Safety Authority; FAA = Federal Aviation Authority; CASA = Australian Civil Aviation Safety Authority; MD = major depression; BD = bipolar disorder.

* Acceptance possible only in rare cases after careful evaluation.

who apply only for sport pilot licenses in the United States. It will be required that only a driver's license is valid and no additional aviation-related requirements are set. A careful examination of lifetime psychiatric symptoms and earlier medical records is advisable if a pilot's fitness to fly due to any psychiatric symptoms or mental distress is unclear. In some cases, it might be possible that the patient had been diagnosed as having had a major depressive episode, but he or she is suffering from BD. In these cases, renewed psychiatric consultation may be useful.

Pilot or pilot candidates are not fit to fly after a diagnosis of BD if it is not possible to find a pharmacological triggering factor causing symptoms that can be treated or eliminated. This exclusion is because of significantly increased risk of incapacitation, especially during mania. The Australian Civil Aviation Safety Authority³ suggests that suicide risk among bipolar cases is about 10–15% and, in a recent comprehensive review of 79,937 subjects with BD, the suicide risk was even higher.³³ Therefore, it is very difficult to verify a 1% risk rule will be reached in this patient group even if the patient does not have symptoms at the time of the medical examination.²⁶ Moreover, an increased monitoring frequency does not necessarily help in reducing this risk. The high-risk recurrent new episodes of BD are the basis for the aeromedical decision that BD patients are not fit to fly.

In conclusion, this study shows that the demarcation of psychiatric disorder related to fitness to fly is an important step in safety. In some rare cases, pilots believed to have a major depressive episode may in fact suffer from BD. Obviously a risk analysis should be performed. Prevention is the best approach to reduce aircraft accidents. In addition to periodic health examinations, especially in commercial aviation, there is a need to better document current medical treatments. These practices will improve awareness of the pilot's health and allow for more effective preventive measures.

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