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Assessing Trends in Cannabinoid Concentrations Found in Specimens from Aviation Fatalities between 2007 and 2016

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16. Abstract

Marijuana continues to be the most commonly abused drug in the United States and is known to cause decrements in psychomotor performance. Delta-9-tetrahydrocannabinol (THC), the major psychoactive component of the cannabis plant and its major metabolite, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) are routinely tested for in fatal aviation accident investigations by the forensic toxicology laboratory at the Civil Aerospace Medical Institute (CAMI). This study was initiated to examine the blood cannabinoid concentrations of THC and THCCOOH detected in victims of aviation accidents from 2007–2016 and follows a similar report from CAMI that covered the previous 10-year period (1997–2006) in which it was noted that these cannabinoids were increasing in concentration. There were 2,909 cases received by the Forensic Sciences Section at CAMI during the current study period, 99 of which (3.4%) were positive for THC or THCCOOH in at least one specimen-type (fluid or tissue). When compared with the previous 10-year study, 2007–2016 showed a 433% and 23.5% increase in overall median blood concentration of THC and THCCOOH, respectively. However, over the 10-year period of the current study, the blood concentrations reflected a downward trend. The mean and median THC/THCCOOH concentration ratio was 0.62 (± 0.53) and 0.45, respectively, with some individuals having ratios > 1.0. The THC/THCCOOH ratios trended upward over the 10-year study period. Fifty-five cannabinoid-positive, medically certificated pilots and 1,918 controls were examined for any relationship between the presence of the cannabinoids and other variables of interest. This examination indicated that cannabinoid-positive pilots tended to be younger in age and were likely to have another impairing drug in their body at the time of the aviation accident. This study contributes much needed data to scant research on postmortem cannabinoid concentrations and will assist with the interpretation of cannabinoid positive cases.

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INTRODUCTION

Cannabis sativa (marijuana) is the most commonly used illicit drug, with global reports of approximately 183 million people (3.8%) using the drug at least once in 2015.[1] In the United States, the 2015 National Survey on Drug Use and Health indicated that there was an estimated 22.2 million people (8.3%), aged 12 and older, that used marijuana in the past month. A significant number (4.0 million) had a past year Substance Abuse Disorder related to marijuana use.[2] In 2011, marijuana contributed to 146.2 emergency room visits per 100,000 people with the greatest number of visits from the age group of 21–24 year olds.[3]

The legality of cannabis worldwide has been changing since the late 1990s with many countries decriminalizing the drug or allowing its use for medical and recreational purposes. Although the U.S. government continues to maintain the drug as a Schedule I substance under the Controlled Substances Act, state laws have changed in the past few decades to allow more widespread use. Beginning in 1996, states passed their own legislation allowing marijuana to be used for various medical conditions and in 2012, the first two states, Colorado and Washington, passed statutes to permit recreational use of marijuana. As of April 2017, eight states and Washington DC have laws in place for residents to consume marijuana for recreational purposes, and 18 additional states allow the use of marijuana for medical purposes.[4,5]

These legislative changes add to the already extensive use of the drug, making cannabis a public health concern. A recent study examined recreational use of marijuana before and after legalization for college undergraduates at Washington State University. The authors demonstrated that prevalence of marijuana use and average frequency of use by college undergraduates significantly increased after recreational marijuana legalization.[5] Colorado records show that cannabis is responsible for a twofold increase in visits (85 to 186 visits per 10,000 people) to urban hospitals for non-Colorado residents from 2013 to 2014.[6]

The main psychoactive component of cannabis, Δ9-tetrahydrocannabinol (THC), has been frequently investigated over the last five decades and causes effects including euphoria, relaxation, and altered perception.[7] THC and its inactive metabolite 11-nor-9-carboxy-Δ^9-tetrahydrocannbinol (THCCOOH) are common substances detected in driving under the influence of drugs (DUID) cases due to the high prevalence of cannabis. The 2013–2014 National Highway Traffic Safety Administration (NHTSA) National Roadside Survey (NRS) reported a 48% increase in the weekend nighttime drivers testing positive for THC, with a change from 8.6% in 2007 to 12.6% in the 2013–2014 study.[8]

Psychomotor effects of cannabis on driving have been reported to include increased reaction times, loss of coordination, and impairment of divided attention tasks. A study that compared fatal and nonfatal road traffic collision (RTC) victims suggests that cannabis plays a greater role in fatal road traffic collisions. THC concentrations were significantly higher in fatal RTC victims than nonfatal RTC victims ($p = 0.01$).[9] Furthermore, in a case-control study with drivers fatally injured in motor vehicle crashes (cases) and drivers not involved in an accident in the 2007 Roadside Survey (controls), prevalence of marijuana was higher (12.2%) in the cases compared with 5.9% in the controls ($p < 0.0001$).[10] However, the authors demonstrated alcohol was a significant effect modifier on the association of marijuana use and fatal motor vehicle accidents. Using drivers testing negative for both marijuana and alcohol as the reference, the calculated odds ratio was 1.54 (95% CI 1.16–2.03) for those cases testing positive for marijuana but negative for alcohol, controlling for age, sex, and geographical region in the model. Using the same group testing negative for both as the reference, the adjusted odds of being fatally injured increased more than 16-fold (95% CI 14.23–18.75) for the group testing positive for alcohol but negative for

marijuana, and over 25-fold (95% CI 17.97–35.03) for those testing positive for both. Therefore, additional studies are needed to address the combined effects of alcohol and marijuana on fatal accidents.

Li et al. performed a meta-analysis of 9 epidemiologic studies that assessed the association between marijuana use and crash risk.[11] Of the 9 studies reviewed, 5 were case-control studies, 2 were cross-sectional, and 2 were cohort studies. The authors extracted data and calculated unadjusted odds ratios for each study. The odds ratios for all studies except one reported a statistically significant increase in risk of motor vehicle crash. The overall summary odds ratio generated for the 9 studies was 2.66 (95% CI 2.07–3.41), indicating consistent evidence of significantly higher odds of crash involvement for drivers that used marijuana compared with drivers who did not.[11] However, the level of heterogeneity between the 9 studies was high ($I^2 = 79.1$), and thus future studies are needed to confirm the degree of risk between marijuana and transportation accidents. Li et al. also identified a dose-response relationship between THC concentration and fatal crash involvement from data provided by one of the nine studies.[12] The authors of this case-control study used urine samples of fatally injured motor vehicle cases in Quebec from 1999 through 2001 and compared the results with urine samples of randomly selected participants from roadside surveys in Quebec's driving population. Using drivers with no THC detected in the samples as the reference, the odds of having low, medium, and high concentrations of THC were 1.1 (95% CI 0.5–2.6), 1.8 (95% CI 1.0–3.5), and 3.3 (95% CI 1.9–5.9) times higher in those fatally injured compared with controls not involved in accidents, respectively, although the confidence intervals were wide and included 1.0 in all but the highest category.

A study performed by NHTSA evaluated the prevalence of alcohol, drugs, and marijuana in Washington state drivers at three different times surrounding the legalization of recreational marijuana: Wave 1—prior to legal sales, Wave 2—six months after legal sales, and Wave 3—one year after legal sales. The study demonstrated that prevalence of THC-positive drivers increased, though not significantly, from Wave 1 (14.6%, 95% CI 11.9–17.8) to Wave 2 (19.4%, 95% CI 16.4–22.8) to Wave 3 (21.4%, 95% CI 17.5–25.9). The prevalence of THC-positive in addition to any other drug was 5.9% (95% CI 3.9–8.8), 6.3% (95% CI 4.4–9.0) and 8.9% (95% CI 5.4–4.2) for Waves 1, 2, and 3, respectively. The prevalence of both alcohol and THC in this study was 8.5% (95% CI 3.8–18.0) for Wave 1, 2.2% (95% CI 0.6–7.0) for Wave 2, and 6.2% (95% CI 2.9–12.6) for Wave 3.[13] Another longitudinal study examined 1,265 New Zealand children over a 25-year period, and the authors discovered an association between cannabis use and other illicit drug use. The authors reported increased risk, abuse, and dependency of other illicit drugs in those individuals that were chronic or heavy cannabis users. However, testing for cannabis and other illicit drug use is complex and the researchers noted that the models used may have resulted in an overestimation of the causal linkages.[14] Thus, more studies to identify links between cannabis and other illicit drug use would be beneficial.

Reports have also demonstrated that the average THC content in confiscated marijuana from the U.S. has increased over the last two decades from about 4% in 1995 to 12% in 2014.[15] The higher THC content raises concerns for the public health regarding mental health issues, hospital visits, and dependency. A greater risk of psychosis has been associated with individuals who are frequent cannabis users and those who use the higher potency cannabis products.[16] Furthermore, in a study evaluating use of cannabis with varying amounts of THC, those who smoked the high-potency type demonstrated an increased likelihood of dependence, with 38% of the individuals in this group meeting the criteria for cannabis dependence.[17]

Due to the low acute toxicity and the long-held belief that cannabis does not directly cause death, there has been a lack of data and research regarding cannabinoids in postmortem cases. However, with the continued popularity and changes in legal status of the drug, recent publications have focused on postmortem distribution and redistribution of various cannabinoids. Gronewold and Skopp evaluated concentrations of THC along with its equipotent metabolite, 11-hydroxy-THC (11-OH-THC), cannabinol, cannabidiol, THCCOOH and its glucuronide in five postmortem cases in one of the first investigations regarding distribution of cannabinoids. In the cases presented by the authors, THC concentrations ranged from 0.6–1.9 ng/mL in heart blood in four cases, and one case

had a THC concentration in femoral blood of 2.5 ng/mL. THCCOOH concentrations in heart blood ranged from 9.2–18 ng/mL and the THCCOOH concentration in femoral blood was 13.7 ng/mL.[18] Because this was one of the first papers to report postmortem concentrations of THC and THCCOOH, future studies should attempt to replicate these findings.

THC is highly lipophilic with a large volume of distribution (10 L/kg), thus the drug would appear to be a good candidate for extensive postmortem redistribution (central:peripheral blood ratio > 2). However, two reports that have addressed the postmortem redistribution of THC, THCCOOH, and 11-OH-THC have produced results inconsistent with that expectation. Holland et al. examined 19 medical examiner cases and found a slight degree of postmortem redistribution with median central:peripheral blood ratios of 1.5, 1.7, and 1.8 for THC, 11-OH-THC, and THCCOOH, respectively. Moreover, the authors assessed postmortem interval as a significant interaction in the model, with increasing time from death to autopsy resulting in an increasing trend of postmortem redistribution.[19] Lemos and Ingle analyzed THC, 11-OH-THC, and THCCOOH in blood and urine of 30 postmortem cases and found a modest degree of postmortem redistribution with mean central:peripheral blood concentration ratios of 0.62, 0.99, and 1.07, respectively.[20]

The Federal Aviation Administration's Civil Aerospace Medical Institute (CAMI) has also published three articles on postmortem cannabinoid concentrations. The most recent of which is a detailed distribution of THC, 11-OH-THC, and THCCOOH in postmortem fluids and tissues by Saenz et al.[21] Canfield et al. evaluated concentrations of THC and THCCOOH found in urine and blood from fatal aviation accidents between 1997–2006 and reported that the median THC concentration increased from 0.5ng/mL in 1997–2001 to 2.0 ng/mL in 2002–2006 (p=0.0103), which paralleled the increase in THC potency for that time period.[22] Kemp et al. described the postmortem fluid and tissue distribution of THC and THCCOOH in aviation accident pilot fatalities between 2005 and 2012. The reported median THC blood concentration for this study was 5.0 ng/mL and lung and heart proved to be useful specimens for detection of cannabinoids.[23] While these two studies contribute to the current research regarding increases in THC concentration, an updated study needs to be conducted to address gaps in the literature for more recent years. Thus, the aims of this study are to provide additional data on cannabinoid concentrations from postmortem cases by evaluating the concentration of THC and THCCOOH found in fatal aviation accidents from 2007–2016 and to evaluate any associations between potential exposures and marijuana-related pilot fatalities.

METHODS

Previous publications provide details of sample submission procedure to the CAMI forensic toxicology laboratory.[24] Briefly, biological specimens are sent to CAMI in kits designed specifically for toxicological analysis of aviation accidents. The samples were stored frozen (-20°C) until analysis. Blood and tissue specimens were screened for cannabinoids by enzyme-linked immunosorbent assay (Immunalysis Corp, Pomona, CA) with a cutoff of THCCOOH of 15 ng/mL in blood and 40 ng/g in tissue. Urine specimens were screened by chemiluminescence on the ARCHITECT c4000 system (Abbott Labs, North Chicago, IL) with a cutoff concentration of THCCOOH of 25 ng/mL. The confirmation and quantitation of THC and THCCOOH in blood or tissues is a solid phase extraction followed by analysis on a gas chromatography/mass spectrometry (GC/MS) in negative-ion chemical ionization mode. The urine samples were extracted similarly but included a hydrolysis step and the analysis was performed by GC/MS using electron impact ionization (EI). The limit of quantitation for each method was 1.0 ng/mL. The details of the method used at CAMI can be found in a previously published article.[25]

A 10-year period from 2007–2016 was selected as the timeline for this study to follow-up on published data reporting the same results from 1997–2006. Cannabinoid concentrations in blood for all people whose specimens were evaluated in the laboratory were compared over the 10-year time period. Due to the low number of fatal accidents involving cannabis each year, results from 2007–2011 and 2012–2016 were combined to evaluate trends in blood cannabinoid concentrations. Because the THC concentrations were not normally distributed, the two

distributions were evaluated using the Wilcoxon-Mann-Whitney test in SAS v.9.4 with an assumed alpha of 0.05. The researchers also quantified the ratio of THC to THCCOOH in all blood samples that had both concentrations (n = 52). The ratios were also separated into the two 5-year periods for statistical analysis.

Additional analyses were conducted to evaluate the association between potential exposures and marijuana-related pilot fatalities in a case-control study among medically-certificated aviation pilots during 2007–2016. The researchers linked records collected from two separate FAA databases, the Document Imaging Workflow System (DIWS), which includes medical certification data for all pilots, and CAMI's Forensic Toxicology Database, which includes demographics and toxicology results from human specimens received from most of the fatal U.S. civil aviation accidents every year. Eligible study participants for this portion of the analyses were restricted to all US pilots aged 18 years or older who had a fatal accident with specimens examined in the toxicology laboratory during the study period and held a valid medical certificate at the time of the accident.

Outcomes of the case-control study were fatal accidents in which the pilot was determined to have THC or THCCOOH in any tissue or specimen. The pilots in the case-control study identified from the toxicology database were linked back to DIWS to obtain exposure and covariate data. Exposure variables were obtained from the airman's most recent medical exam in DIWS prior to the pilot's fatal accident. This was an exploratory analysis, so no variables were identified a priori to include in the final model. Instead, the researchers examined all potential exposures collected from the pilots' most recent medical examinations, which included sex, body mass index (BMI), age at accident (calculated from date of birth and date of the accident), self-reported total flight time, self-reported flight time in the last six months, issued medical class (first-, second-, or third-class), effective medical class, and geographical region of residence.

Although various medical standards for the three medical classes have changed over the years, the concept of three classes with varying degrees of medical standards is currently used to medically certify pilots. Authority for these requirements comes from the Code of Federal Regulations (CFR) parts 61 and 67.[26,27] The three classes of medical certificates are 1) First-class: This class requires the most stringent medical examination. Airline transport pilots (ATPs) need to hold a first-class certificate to fly. 2) Second-class: Commercial pilots (who are not the pilot-in-command), commercial non-airline duty pilots, flight engineers, and flight navigators need to hold at least a second-class certificate to fly. 3) Third-class: Most private pilots, recreational pilots, and student pilots need to hold at least a third-class certificate to fly. Once the validity period for one class has expired, it rolls into the next class. For instance, a certificate can be *issued* as a first-class, and become automatically valid as a second-class as the first-class validity period expires. If the person continues to not renew his/her certificate, the *effective* class of the certificate would then roll into a third-class once the validity period of the second-class expires. Once a third-class certificate expires, the certificate is no longer valid and with few exceptions, the airman would be flying illegally.

A statement of demonstrated ability (SODA) indicated that an airman possessed a waiver that he or she was fit to fly with a permanent disability. A special issuance indicated that an airman possessed a waiver for a specific medical condition. Total flight time, flight time in the last six months, age at accident, and BMI were first examined as continuous variables. In the absence of linearity association, the continuous covariates were categorized for analysis. BMI was categorized as < 25 for underweight/normal, 25–29.9 for overweight, and ≥ 30 for obese. Categories for age, total flight time, and flight time in the last six months were defined by tertiles based on the distribution of the controls in the study population. Finally, the presence of ethanol and other impairing drugs besides THC were examined from the toxicology database as potential exposures in the model. The presence of ethanol was determined by review of case history and laboratory data to exclude cases showing evidence of postmortem ethanol production. The list of impairing drugs included in the analyses is found in Table 1.

Table 1. List of impairing drug found in pilot fatalities, 2007–2016.

Alprazolam	Citalopram	Hydrocodone	Oxymorphone
Amitriptyline	Clonazepam	Hydromorphone	Pentobarbital
Amphetamine	Clozapine	Hydroxyalprazolam (Alpha-)	Pheniramine
Benzoylecgonine	Cocaethylene	Hydroxyzine	Phenmetrazine
Brompheniramine	Cocaine	Lorazepam	Phenobarbital
Buprenorphine	Codeine	Meclizine	Phenylpropanolamine
Bupropion	Cyclobenzaprine	Methadone	Promethazine
Butalbital	Diazepam	Methamphetamine	Propoxyphene
Carbamazepine	Dihydrocodeine	Methylone	Temazepam
Carisoprodol	Diphenhydramine	Morphine	Tramadol
Cetirizine	Doxylamine	Nordiazepam	Trazodone
Chlordiazepoxide	Fentanyl	Oxazepam	Zolpidem
Chlorpheniramine	Gabapentin	Oxycodone	Zopiclone

Statistical analyses were conducted using SAS v.9.4. There was a total of 55 cases positive for cannabinoids and 1,918 controls (negative for cannabinoids) in the dataset. Crude and multivariate logistic regression models were used to calculate unadjusted and adjusted odds ratios (ORs) and 95% CIs. Covariates were assessed for confounding by adding them one by one using forward selection to evaluate whether addition of selected covariates met the criteria for confounding by altering the OR by more than 15%. Evaluation of effect modification was performed by adding interaction terms into the models and retaining those that had a p-value of less than 0.05.

RESULTS

Of the 2,909 individuals from fatal accidents tested in the laboratory during 2007–2016, a total of 99 (3.4%) individuals had at least one specimen that tested positive for THC or THCCOOH. However, when the researchers restricted the specimens to blood samples, only 74 cases, containing one or both cannabinoids examined in this study, remained for the initial analysis.

Of the 74 total cases, 71 were from males, and 3 were from females. The mean age of the males and females at the time of accident was 46.0 and 43.2 (SD = 13.8 and 15.6), respectively. The overall median THC concentration in the blood for the 10-year period was 8.0 ng/ml (range = 1.3–69.2), while the median THCCOOH concentration was 10.5 ng/ml (range = 1.2–200.5). See Table 2 below. Scatterplots of THC and THCOOH concentration distributions throughout the 10-year period in Figures 1 and 2 demonstrate the clusters of concentrations as well as the outliers in each year.

Table 2. Mean and Median THC and THCCOOH concentrations in blood samples by year.

Year	THC (ng/ml)					THCCOOH (ng/ml)				
	N	Mean	SD	Median	Range in Blood	N	Mean	SD	Median	Range in Blood
2007	5	18.3	14.7	12.6	4.5–39.7	6	50.5	47.4	41.9	3.7–128.0
2008	7	30.8	26.3	31.1	3.1–69.2	8	46.1	64.8	30.7	2.7–200.5
2009	7	12.8	10.7	7.5	3.2–34.2	10	45.2	44.3	21.3	1.2–112.6
2010	4	7.2	6.5	4.5	3.1–16.9	5	12.6	8.8	10.4	1.6–25.5
2011	4	9.0	5.5	8.0	3.5–16.6	6	15.1	14.3	13.6	1.6–32.5
2012	2	8.3	7.9	8.3	2.7–13.9	5	10.9	7.6	7.1	5.4–23.9
2013	6	10.4	11.7	6.7	2.1–33.7	7	27.1	43.5	9.6	2.0–124.3
2014	6	5.6	3.9	5.3	1.3–10.7	8	21.2	23.0	14.5	1.5–63.2
2015	5	6.3	5.0	3.6	2.8–14.3	9	13.0	21.2	4.6	2.0–68.6
2016	6	17.5	19.5	10.4	4.5–56.9	10	9.9	7.8	7.3	1.7–24.8
Total	52	13.7	15.4	8.0	1.30–69.2	74	25.8	36.4	10.5	1.2–200.5

Figure 1. Scatter plot (with overall regression line) of THC concentrations by year (ng/mL).

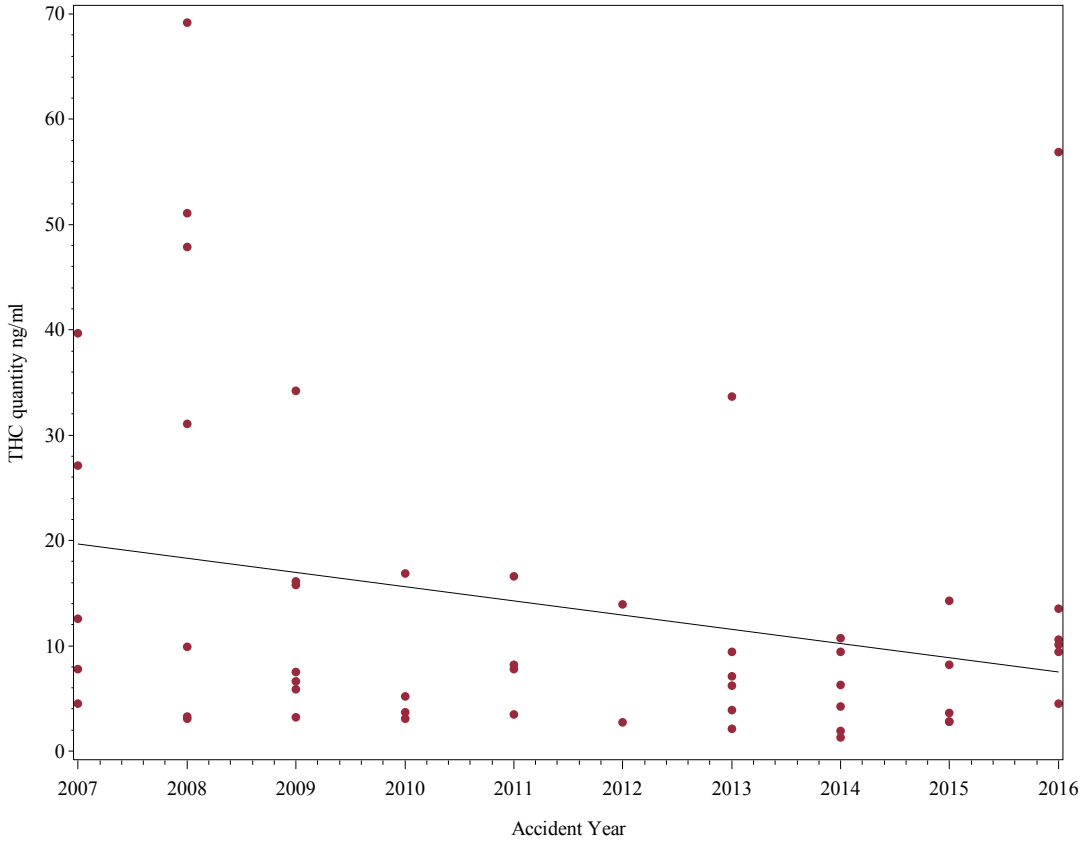
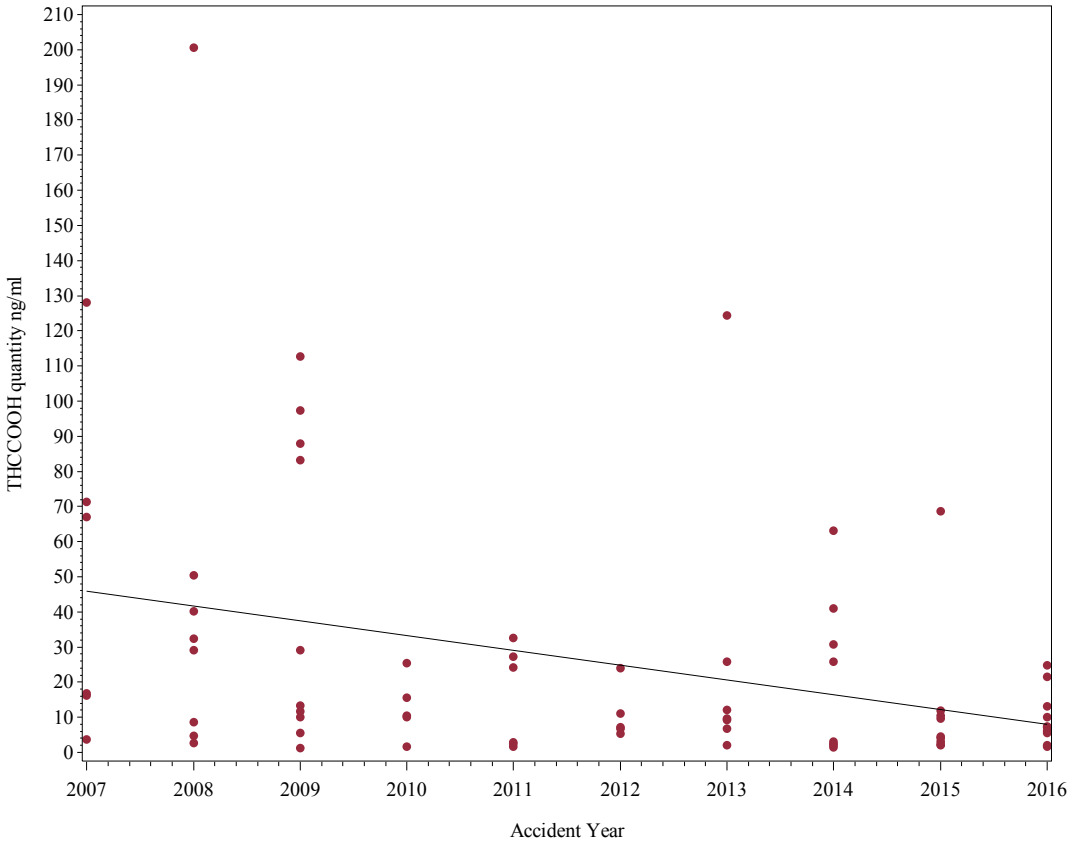


Figure 2. Scatter plot (with overall regression line) of THCCOOH concentrations by year (ng/mL).



When the quantities were categorized into the two 5-year time periods, the median THC concentration for 2007–2011 was 8.2 ng/ml (range = 3.1–69.2), while the median THC concentration for 2012–2016 was 7.1 ng/ml (range = 1.3–56.9). The distributions of the two periods were not statistically different from one another (Figure 3, p = 0.1030). The median THCCOOH concentration for 2007–2011 was 16.7 ng/ml (range = 1.2–200.5), and was statistically higher than the median THCCOOH concentration of 7.4 ng/ml (range = 1.5–124.3) for 2012–2016 (Figure 4; $p = 0.0155$).

Figure 3. Distributions of two 5-year time periods for THC blood concentrations (ng/mL).

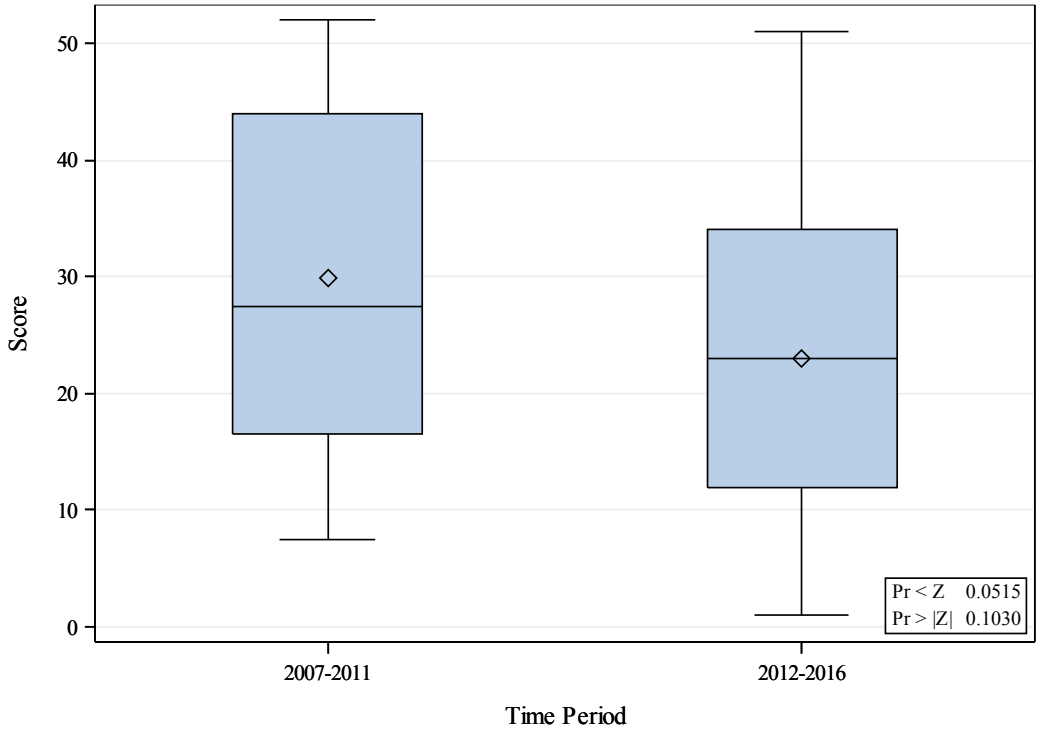
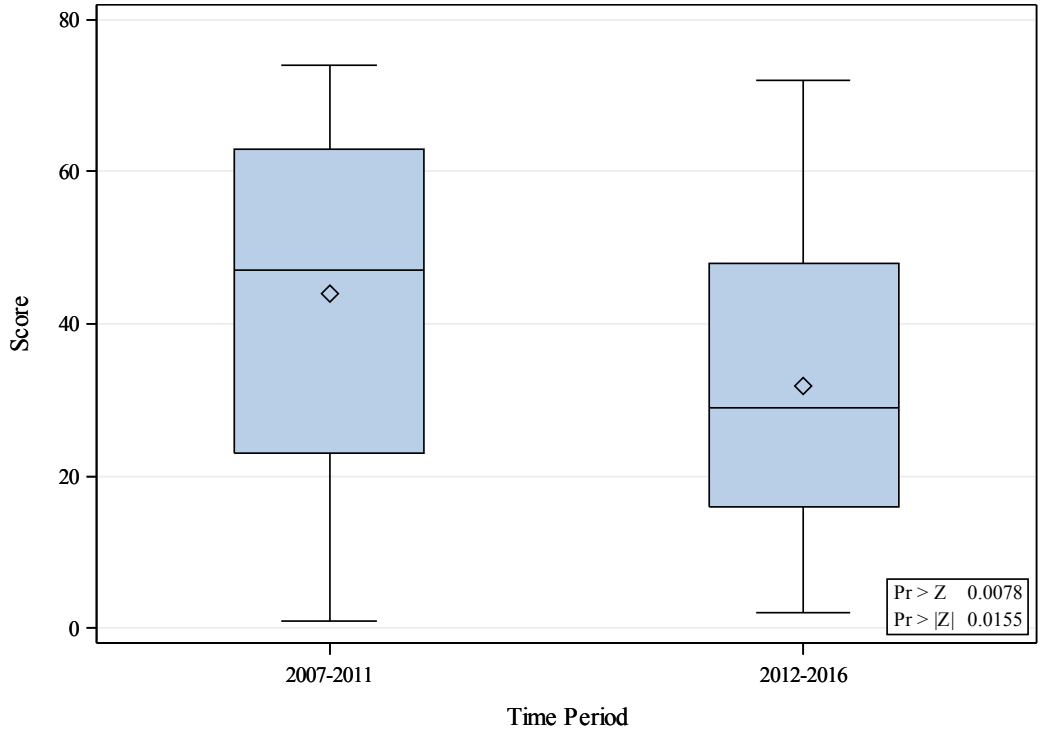


Figure 4. Distributions of two 5-year time periods for THCCOOH blood concentrations ng/mL).



The researchers repeated the above analyses, quantifying the ratio of THC to THCCOOH in all blood samples that had both concentrations. Overall, there were 27 samples with both THC and THCCOOH between 2007 and 2011 and 25 samples for the 2012–2016 period (Table 3). The median ratio for 2007–2011 was 0.38 (range = 0.06–2.19) while the median ratio for 2012–2016 increased to 0.58 (range = 0.12–2.65). However, the increase in concentration ratios for the two periods was not statistically different (Figure 5; p = 0.3793). Figure 6 demonstrates the gradual rise in ratio concentrations over the ten-year period, although there are outliers in several years influencing the overall mean values for those years.

Table 3. Mean and median THC/THCCOOH concentration ratios in blood.

Year	Ratio of THC to THCCOOH				
	N	Mean	SD	Median	Range of ratios
2007	5	0.40	0.26	0.40	0.06–0.78
2008	7	0.77	0.52	0.65	0.20–1.58
2009	7	0.32	0.14	0.32	0.14–0.50
2010	4	0.51	0.41	0.41	0.15–1.08
2011	4	0.85	0.91	0.49	0.24–2.19
2012	2	0.54	0.06	0.54	0.50–0.58
2013	6	0.62	0.34	0.59	0.27–1.05
2014	6	0.36	0.27	0.22	0.16–0.79
2015	5	0.53	0.43	0.34	0.12–1.20
2016	6	1.25	0.84	0.88	0.43–2.65
Totals	52	0.62	0.53	0.45	0.06–2.65

Figure 5. Scatter plot (with overall regression line) of THC/THCCOOH blood concentration ratios (N = 52).

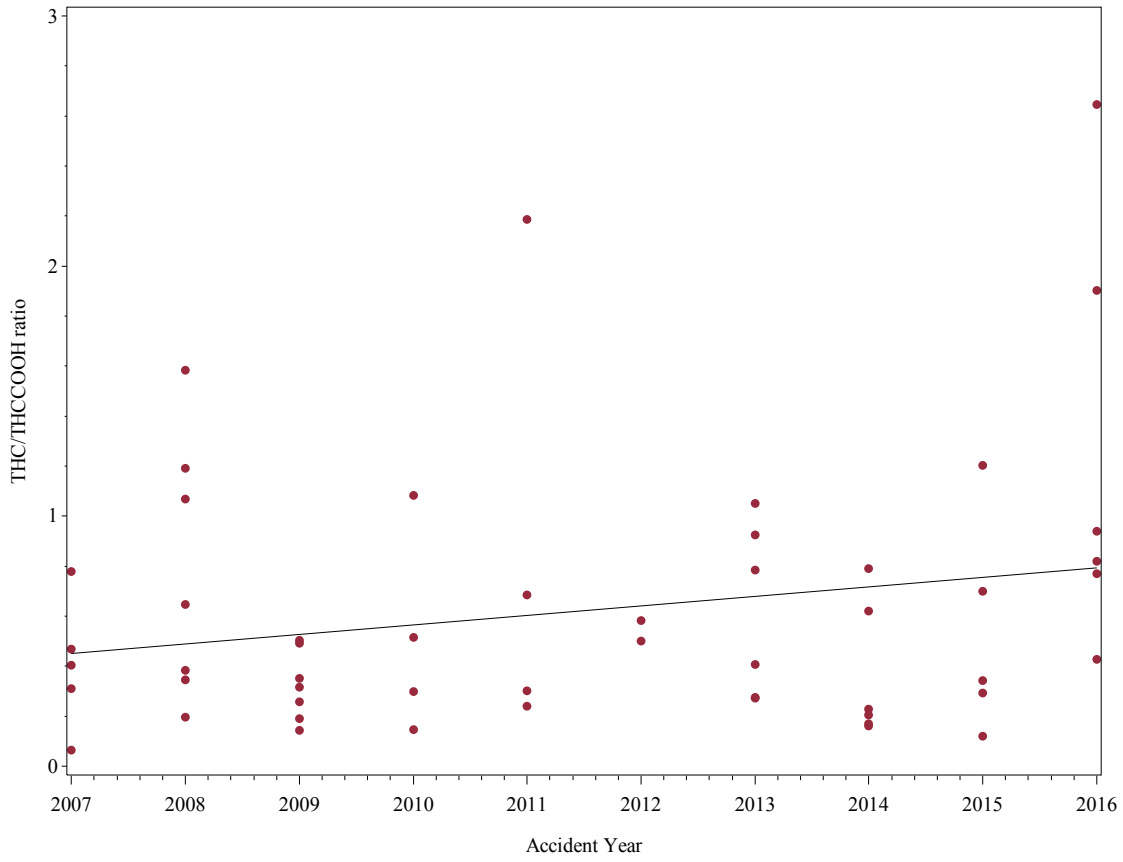
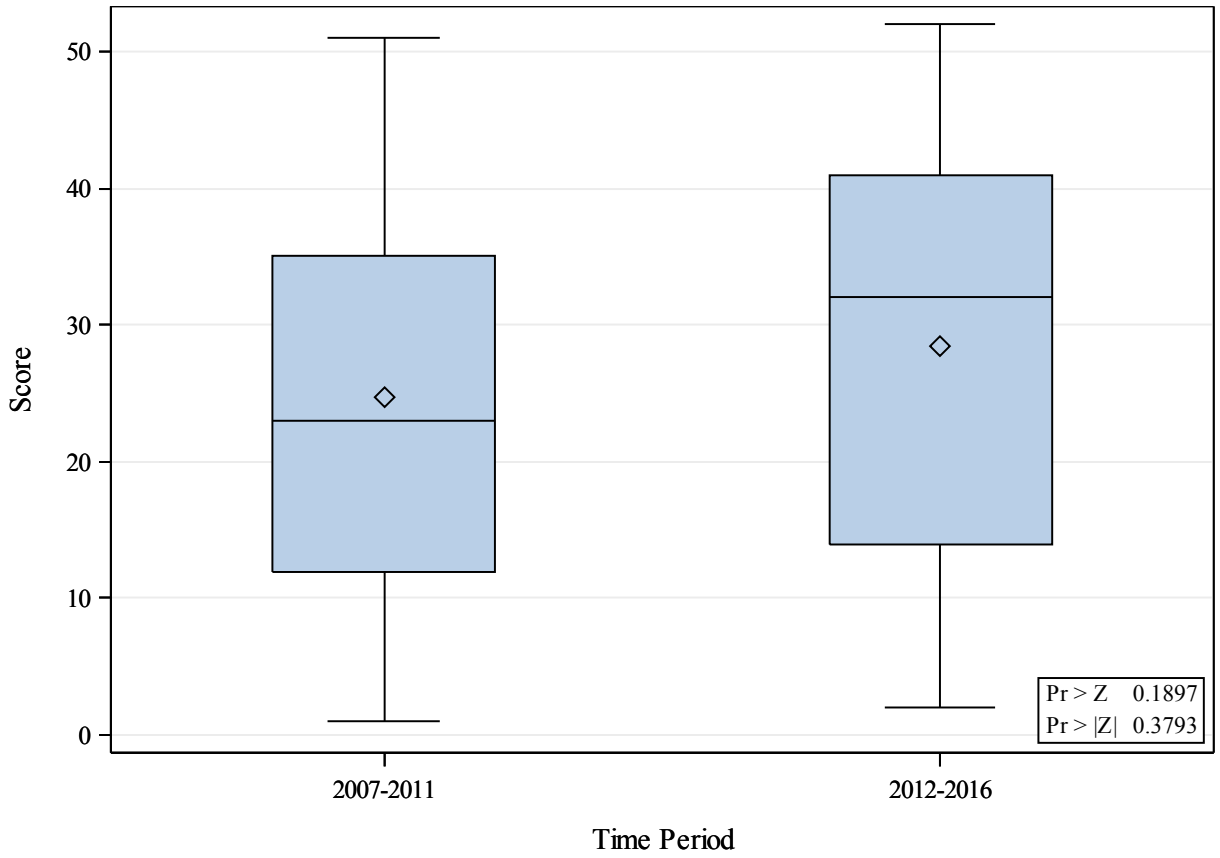


Figure 6. Distribution of THC/THCCOOH blood concentration ratios for two 5-year time periods.



For the second part of the study, 55 pilot cases were identified with THC or THCCOOH in their system who held valid medical certificates at the time of their fatality, and 1,918 deceased pilot controls were identified who did not test positive for THC or THCCOOH but held valid medical certificates at the time of accident. The investigation indicated that the mean age for the cases was 46.8 years (SD = 13.01), while the mean age of the controls was 53.9 (SD = 14.5), with ages ranging from 18 to 90 years.

With the exception of age at time of the accident and the presence of other impairing drugs, the distribution of cases and controls were similar across most of the exposure categories (Table 4). The unadjusted odds of having at least one impairing drug in the pilot's system were 2.04 (95% CI 1.15–3.63) times higher in pilots who tested positive for THC or THCCOOH compared with the controls. Using pilots aged 61 and older as the reference, the odds of being ages 48–61 and 18–48 were 2.35 times (95% CI 1.02–5.39) and 3.61 times (95% CI 1.63–7.97) higher in positive cases compared with controls, respectively (Table 4). When multivariate analysis was performed with these two variables as exposures in the model together, the odds of cases having at least one impairing drug increased to 2.33 (95% CI 1.30–4.16) times that of controls, and the OR of cases aged 48–61 and 18–48 increased to 2.42 (95% CI 1.05–5.59) and 3.99 (95% CI 1.80–8.89) using those aged 61 and older as the reference.

No covariates met the criteria for confounding when added to the models with age or impairing drugs. Finally, no significant interactions between the age, impairing drugs, and the other covariates were observed.

Table 4. Study Population and Characteristics Among Cases and Controls

Variables	Cases N = 55 (%)	Controls N = 1918 (%)	Unadjusted OR and 95% CI
Sex			
Male	55 (100.0)	1865 (97.2)	N/A+
Female	0.0 (0.0)	53 (2.8)	Referent++
Ethanol Present			
Yes	1 (1.8)	66 (3.4)	0.52 (0.07, 3.81)
No	54 (98.2)	1852 (96.6)	Referent
Other Impairing Drugs Present			
Yes	18 (32.7)	369 (19.2)	**2.04 (1.15, 3.63)**
No	37 (67.3)	1549 (80.8)	Referent
Class Issued			
1st	6 (10.9)	307 (16.0)	Referent
2nd	22 (40.0)	651 (33.9)	1.73 (0.69, 4.31)
3rd	27 (49.1)	960 (50.1)	1.44 (0.59, 3.52)
Effective Class			
1st	2 (3.6)	216 (11.3)	Referent
2nd	19 (34.6)	575 (30.0)	3.57 (0.82, 15.45)
3rd	34 (61.8)	1127 (58.8)	3.26 (0.78, 13.67)
Region of Residence on Last Medical#*			
Midwest	5 (9.26)	333 (17.6)	0.54 (0.20, 1.45)
Northeast	8 (14.8)	227 (12.0)	1.26 (0.55, 2.92)
South	22 (40.7)	653 (34.5)	1.21 (0.65, 2.25)
Western	19 (35.2)	680 (35.9)	Referent
Presence of Special Issuance			
Yes	1 (1.8)	185 (9.7)	0.17 (0.02, 1.26)
No	54 (98.2)	1733 (90.4)	Referent
Statement of Demonstrated Ability			
Yes	0 (0.0)	44 (2.3)	NA+
No	55 (100.0)	1847 (97.7)	Referent
Age at Accident (in years)			
18–48.2	28 (50.9)	624 (32.5)	**3.61 (1.63, 7.97)**
48.3–61.4	19 (34.6)	651 (33.9)	**2.35 (1.02, 5.39)**
>61.4	8 (14.6)	643 (33.5)	Referent
Total Flight Time**			
1–765 hours	22 (42.3)	613 (32.7)	1.87 (0.92, 3.81)
766–3150 hours	18 (34.6)	638 (34.0)	1.47 (0.70, 3.07)
>3150 hours	12 (23.1)	624 (33.3)	Referent
Flight Time in Past 6 Months of Exam***			
0–30 hours	22 (43.1)	609 (32.7)	1.31 (0.69, 2.49)
31–86 hours	12 (23.5)	639 (34.3)	0.68 (0.32, 1.44)
>86 hours	17 (33.3)	617 (32.2)	Referent
Body Mass Index^			
Underweight/Normal (<25 kg/m^2)	19 (34.6)	463 (24.2)	1.60 (0.78, 3.27)
Overweight (25–29.9 kg/m^2)	23 (41.8)	948 (49.5)	0.94 (0.47, 1.88)
Obese (≥30 kg/m^2)	13 (23.6)	506 (33.1)	Referent

+No exposure in Case group to compare with controls
++ Referent = All other levels of each variable are compared with this baseline level
# Midwest Region included IA, IL, IN, KS, MI, MN, MO, DN, NE, OH, SD, WI; Northeast region included CT, DC, DE, MA, MD, ME, HN, NJ, NY, PA, RI, VA, VT, WV; South region included AL, AR, FL, GA, KY, LA, MS, NC, NM, OK, SC, TN, TX; Western region included AK, AZ, CA, CO, HI, ID, MT, NV, OR, UT, WA, WY
*Missing 26
**Missing 46
***Missing 57
^ Missing 1

DISCUSSION

Interest in postmortem cannabinoid concentrations in biological fluids and tissues has grown due to the increasing legalization of medical and recreational marijuana use in the U.S. Law enforcement agencies, medical examiners, and other interested parties desire more research on postmortem cannabinoids for case interpretation. The FAA and the National Transportation Safety Board (NTSB) investigate aviation accidents and need postmortem drug testing to determine if cannabinoids may have caused or contributed to a fatal accident. This study was undertaken to follow-up on a previous 10-year study that noted increasing cannabinoid concentrations in fatally injured pilots found during routine toxicology testing at CAMI.

The overall cannabinoid positive proportion for deceased individuals tested at CAMI during fatal aviation accident investigations did not change from 1997 to 2016. The percentage of individuals found to be positive for THC or THCCOOH in at least one specimen (fluid or tissue) from 2007 to 2016 was 3.4% (99 of 2,909 tested). This proportion is identical to that found in the previous 10-year period from 1997 to 2006 (95 of 2,769 tested).

Table 1 demonstrates one of the difficulties in interpreting postmortem cases involving the use of marijuana. In many of the THC-positive cases in this study, 1 or more other impairing drugs were also present. The other drugs represent a broad range of over-the-counter medications, prescription medications, and illegal drugs. Drugs such as fentanyl and morphine must be interpreted with caution, as these may have been administered by emergency personnel during life-saving measures performed on the victim. Oxymorphone may be either a drug itself, administered for pain, or it may be the metabolite of oxycodone, also present on the list.

Interpretation of blood concentrations

The current study focused solely on postmortem blood concentrations of THC and THCCOOH. This reduced the number of cases for the study from 99 to 74 (71 males and 3 females). The excluded 15 cases did not have a blood specimen available for testing. Often in aviation accident investigations, CAMI only receives non-blood fluids (e.g., vitreous fluid, urine, bile) and tissues (liver, kidney, muscle, etc.). This may be due to fire or damage to the body.

Blood concentrations of cannabinoids are used to determine not only the use of marijuana, but also to determine behaviors including psychomotor impairment that may have resulted in an accident. As a result, blood concentrations that are being used to establish legislative limits such as Driving Under the Influence laws similar to the work done with alcohol. Postmortem specimens, however, present complications that must be considered when interpreting such behaviors and impairment. After death, changes in concentration may occur in blood and other biological sample types due to a well-studied phenomenon called postmortem redistribution.[28] This effect has been described elsewhere and presents forensic toxicologists with an interesting challenge when interpreting postmortem cases. The results from studies such as this report, therefore, must be interpreted with caution in light of this phenomenon.

The blood concentrations found in fatal aviation accidents in this study are displayed in Table 2. The data are graphically represented in Figures 1–4. The overall difference in median blood concentrations of THC represents an 433% increase between the back-to-back 10-year periods. For THCCOOH, median blood concentration for 2007–2016 revealed a 23.5% increase over the median concentration for the 1997–2006 period.

The increase in 10-year mean and median blood THC and THCCOOH concentrations in aviation accidents may be related to a reported increase in potency of various cannabinoid products. A study by the Potency Monitoring Program at the University of Mississippi reported data from the analysis of 46,211 samples seized by law enforcement and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993–2008.[29] Their data showed a significant increase in THC content for all confiscated cannabis preparations from 3.4% in 1993 to 8.8% in 2008. This same research group published another study of 39,000 confiscated samples from 1995–2014

and found that the potency of the marijuana materials reached approximately 12% by 2014 with some specimens reaching 30%.[15] These authors noted a shift from the routine marijuana plant material to the more potent *sinsemilla*. It is not known what type of marijuana was ingested for any of the cases in this study.

The scatterplots in Figures 1 and 2 graphically represent the THC and THCCOOH concentrations found in aviation accidents over the 10-year study period of 2007–2016. The regression lines of these scatterplots seem to indicate a downward trend in blood concentrations over the 10 years of the study. The low numbers of cannabinoid-positive cases each year make the slope of the regression line sensitive to extreme concentrations. The regression lines for the THC and THCCOOH in the current study period, therefore, are heavily influenced by the high concentrations of both cannabinoids found between 2007 and 2009, 2008 having the most extreme values (69.2 ng/mL THC, 128 ng/mL THCCOOH).

The results of the two 5-year comparisons during 2007–2016 are graphically illustrated for THC in Figure 3 and THCCOOH in Figure 4. The first 5-year period showed higher THC and THCCOOH concentrations when compared to the second 5-year period. Thus, the grouped statistical analysis supported the scatterplot regression lines suggesting a downward trend in cannabinoid concentrations over the 10-year study period.

In the past, interest has been generated in the scientific literature regarding the use of the THC/THCCOOH concentration ratio as a potential indicator of recent marijuana use, suggesting that a ratio of greater than 1.0 is indicative of being within an hour of use.[30,31] The current study examined blood THC/THCCOOH concentration ratios in 52 blood samples from aviation accidents that were positive for both compounds (Table 3, Figure 5). It can be noted from the scatterplot data that there are several concentration ratios above 1.0, a proposed marker for recent use. The overall trend line is gradually rising, an interesting finding in light of the downward trend lines for the individual THC and THCCOOH concentrations (Figures 1 and 2). The reason for the increasing THC/THCCOOH ratio is unclear and, when grouped into two 5-year periods for analysis, the slight increase between the two 5-year periods was not statistically significant (Figure 6). Great caution must be used for any interpretation, however, as the majority of the aviation accident blood samples for this study were classified as heart blood or cavity blood and may be subject to contamination from postmortem redistribution.

Evaluation of potential risk factors for deceased, cannabinoid-positive pilots

As another method of examining prevalence of cannabinoids in this pilot population, a statistical analysis was undertaken to examine the relationship between the presence of cannabinoids, specifically THC and THCCOOH, and multiple variables in pilots who held valid medical certificates (Table 4).

The study revealed no cannabinoid-positive pilots were female and only 53 females were found in the control group of 1,918 pilots. The study also found that cannabinoid-positive cases were more likely to be in the younger age group. These results are not surprising. A recent consumer report from Headset, Incorporated, a cannabis industry analytics service, showed that, according to their customer database, the average consumer is primarily male and 37.6 years of age.[32] A University of Michigan study from 2013 showed that the average age of medical marijuana customers at a single clinic was 41.5 (SD = 12.6) years of age.[33]

Another variable of interest in this pilot population was the presence of other impairing drugs (Table 4). The study determined the odds of having another impairing drug were more than twice as high in the cannabinoid-positive pilots as the cannabinoid-negative controls involved in a fatal accident. These results are consistent with previous research showing an increased risk of abuse and dependency of other illicit drugs in heavy cannabis users.[14] Table 1 lists impairing drugs found in the fatally injured pilots. Of note is the fact that over-the-counter, prescription, and illegal substances are all represented in the table. Some of the drugs in the table, such as fentanyl or morphine, may be present as a result of pain management and life-saving measures taken by emergency personnel. Only 1 of 55 cannabinoid-positive pilot fatality cases was also found to be positive for ethanol. This is comparable to previous

research from the state of Washington which showed that drivers being positive for both alcohol and THC was rare.[13]

CONCLUSION

Marijuana use is rising as more states legalize its use for recreational and medical purposes. In addition, the potency of marijuana has increased over the years. As demonstrated by this study, the aviation industry is not immune to this phenomenon as fatally injured pilots continue to test positive for cannabinoids in postmortem fluids and tissues. The mean and median blood concentrations for the 10-year period reported here are higher than those previously reported for the 1997–2006 period, although it is encouraging that the concentration trend decreased over the most recent 10-year period (2012–2016). Work is ongoing at CAMI to characterize the postmortem pharmacology of marijuana to provide information for educating pilots and the flying public about its effects and negative impact on aviation safety.

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