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Comparative Evaluation of Forensic Toxicology Findings, 2012-2016

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16. Abstract

The Civil Aerospace Medical Institute's (CAMI) Forensic Toxicology and Biochemistry Research Laboratories provides forensic toxicology services for the Federal Aviation Administration (FAA) and the National Transportation Safety Board (NTSB). In addition, the FAA's Autopsy Program Team obtains autopsy reports for fatal aviation accidents. These autopsy reports may include toxicology results that have been performed by laboratories other than the FAA. The toxicology results reported by CAMI and those released in external autopsy reports have not previously been compared; therefore, a five-year period was examined to compare these results.

Information from these cases is stored in a database called ToxFlo™. ToxFlo™ was queried for the period from 2012-2016. During this time, CAMI received autopsy reports for 1,415 fatalities and specimens from 1,338 victims. In 756 of these cases, external laboratories performed toxicological analyses. Of the cases that had both CAMI and external toxicology results, 227 cases were positive for one or more drugs and were selected for this study.

Overall, CAMI reported more positive results than external laboratories in five groups of drugs (Impairing/Controlled, Routine over-the-counter (OTC), Cardio Active-Related, Rx Impairing, and Other Drugs). CAMI reported 1,051 positive results from 166 different drugs, while external laboratories reported 327 positive results from 82 different drugs. The Impairing/Controlled Group had the most positives for both CAMI and external laboratories. The relative number of positives between CAMI and the external laboratories was greatest for the Cardio Active-Related Group. Diphenhydramine (Benadryl, Sominex) was the most commonly detected drug by both CAMI and the external laboratories. Ethanol was found positive (≥ 40 mg/dL) in 22 cases by CAMI and the external laboratories. Blood quantitative results were compared for diphenhydramine and ethanol.

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Introduction

The Department of Transportation/Federal Aviation Administration (FAA) has a memorandum of agreement with the National Transportation Safety Board (NTSB) to provide forensic toxicology services and obtain autopsy reports for aviation investigated transportation accidents (1). Under the U.S. Aviation Safety Research Act of 1988, biological specimens collected from pilots fatally injured in civil aviation accidents are shipped to the FAA's Bioaeronautical Sciences Research Laboratory (BSRL) located at the Civil Aerospace Medical Institute (CAMI) in Oklahoma City, OK, for toxicological evaluation.

In the event of a fatal aviation accident, the FAA and the NTSB rely on the local death investigation systems in the United States, both medical examiners (ME) and coroners, to perform autopsy services. We routinely request autopsy services on a pilot, pilot-rated passenger, or anyone else who may have been in control of the aircraft at the time of the accident. Autopsy results from medical examiner/coroner offices are received on approximately 95% of all BSRL cases (2). Occasionally, there are situations where autopsy services are not performed. Some examples of these instances are unrecovered remains, such as lost at sea or inaccessible terrain, or because of observing certain religious requests forbidding autopsies (3).

At the time of the autopsy, the pathologist or autopsy technician will obtain samples and package them for shipping to the BSRL using FAA-provided containers. Some medicolegal systems will perform their own toxicological testing to aid in determining the manner and cause of death, while others may submit samples to outside reference laboratories, and/or rely on the results from the FAA analyses to aid in their own death determination. Laboratories submitting samples will customarily supply copies of these external tests to CAMI at a later date.

Methods

The CAMI laboratory receives biological specimens from fatalities of aviation accidents investigated by the NTSB. Each fatality is given an individual case number and treated independently, even if there are multiple fatalities per accident. CAMI conducts toxicological analyses for the presence of volatile substances, including ethanol, as well as testing for carboxyhemoglobin, cyanide, and glucose. CAMI also looks for drugs, including over-the-counter (OTC), abused, and prescription (Rx) medications. The analyses of these cases assist the

FAA's Office of Aerospace Medicine (AAM), Office of Accident Prevention and Investigation (AVP), and the NTSB in their accident investigation processes.

Demographic information and toxicological results for all cases are stored in a Structured Query Language (SQL) database called ToxFlo™. This study consists of examination of data from pilot fatalities entered into this database.

At the time of receipt of the autopsy reports, the Autopsy Program Team (AUT) abstracts an aggregate of all the findings into the Medical Analysis Tracking Registry (MANTRA™). MANTRA is a SQL database developed by the Aerospace Medical Research Division of CAMI. It serves to support the operational function of tracking and trending autopsy and local medicolegal toxicology reports, support accident investigations, as well as supporting research activities within the FAA.

Upon request, CAMI has always made our toxicology results freely available to laboratories submitting samples to us, and many laboratories have reciprocated in this exchange. No research has been conducted to date, however, that evaluates potential differences in the toxicological findings reported by CAMI and external laboratories.

Our original hypothesis in this evaluation was that there would be no significant reporting differences between our two sets of laboratories. We tested this assumption by searching recent CAMI toxicology and autopsy databases for positive toxicology results, as reported in the five-year period from January 1, 2012, through December 31, 2016.

During this period, the FAA investigated 1,216 fatal accidents involving 1,623 individuals. As previously indicated, these individuals could have been a pilot, a pilot-rated passenger, or any other type of passenger. AUT received 1,415 autopsy reports for fatal victims, and there were 1,303 fatal certificated pilot or pilot-rated passengers in this group.

For the present study, only the 1,303 fatality cases, for which outside toxicology results had been provided, were considered. Therefore, the emphasis of this study was the comparison of drug toxicology results between CAMI and those obtained from external autopsy reports, and to note any differences between the two sets of laboratories.

Reports for prescription and illicit drugs, along with OTC medications, were considered positive if there were either qualitative or quantitative results provided for a particular drug. Ethanol was

considered positive if results were ≥ 40 milligrams/deciliter (mg/dL). This ethanol concentration was selected because FAA regulations state that no person should operate, or attempt to operate, an aircraft if their blood alcohol is at this concentration (4). Carboxyhemoglobin, glucose, nicotine, and cotinine results were excluded from this data query because not all external laboratories perform these types of tests. In addition, as previously stated, this study is solely concerned with the evaluation of potential differences in drug concentrations between the two sets of laboratories.

As discussed below, the local medicolegal system must determine the cause and manner of death in each of their cases. Therefore, the coroners/MEs may deem it unnecessary to perform toxicology services on all aviation accidents. From the total cases (N= 1,338) received by the CAMI toxicology laboratory, there were only 756 (56.5%) cases that had external toxicology services as well. Therefore, 582 cases were not included in this study, because no external toxicology services were available to compare the results.

Results and Discussion

Testing Performed by CAMI

As noted above, there were 756 cases received by the CAMI toxicology laboratory that had external toxicology performed as well (Figure 1). However, due to the lack of appropriate specimens received by CAMI, only 726 cases were tested for alcohol. There were 22 cases analyzed by CAMI in which volatile analysis revealed a positive result of greater than 40 mg/dL.

Drug analysis was performed in 731 of the 756 cases received. Both CAMI and external laboratories had negative results in 324 of these cases. There were 173 cases in which CAMI results were positive; but external laboratory results were negative. There were only seven cases in which CAMI results were negative, but external laboratory results were positive. These small differences in testing results are not unexpected, due to factors such as contamination, specimen type received, etc.

Finally, there were 227 cases in which both CAMI and the external laboratories reported a positive result for drugs, metabolites, and/or related substances. Therefore, there were 400 positive cases reported by CAMI, from the original 731 cases in which drug analysis was performed. These results represent an overall positive rate of 55%. This is quite consistent with

previous CAMI reports showing a positive rate of 48% for aviation accidents cases received in approximately the same time period (5).

In contrast, the 234 cases received from external laboratories represents a positive rate of only 32%. This study focused on the comparison of the 227 cases in which both CAMI and external laboratories produced positive results.

Drugs

Drugs were classified into five main groups: Impairing/Controlled, Routine OTC, Cardio Active-Related, Rx Impairing, and Other Drugs. Drugs were further sub-divided into 40 different drug types. Each drug was categorized according to its status as a parent compound or metabolite, drug type, and the number of cases in which the drug was reported by CAMI and by external laboratories (Table 1). Finally, metabolites were listed as active for those that produce an effect, or inactive for those that do not. In the 227 cases examined, CAMI identified 166 different drugs and generated 1,051 positive reports from them. External laboratories identified 82 drugs and generated 327 reports.

Overall, CAMI reported more positive results than the external laboratories in every one of the five Drug Groups (Figure 2). The Impairing/Controlled Group had the highest number of positives for both CAMI (N= 453) and the external laboratories (N= 206). The greatest difference in reporting frequency was seen in the Cardio Active-Related Group. CAMI reported 197 cases, which was approximately 9.9 times more than external laboratories.

One reason for the differences in the case results may have to do with the respective missions of CAMI and the external laboratories. As previously stated, medical examiners and coroners must determine a cause and manner of death in each of their cases. Due to heavy workloads, toxicology testing may be limited for cases in which these facts are already known. Some examples of these types of ME/coroner cases could include gunshot wounds, drowning, electrocution, decapitation, strangulation, extensive thermal injury, blunt force trauma from a vehicular accident, or falls from a significant height.

For many aviation accidents, the obvious immediate cause of death is blunt force trauma, and the manner of death is accidental. Therefore, the ME/coroner will probably request only toxicology analyses for obviously impairing substances before completing their report. These drugs would

be included in the Impairing/Controlled list (Group 1) discussed below. Because these drugs are of great significance to both CAMI and to external laboratories, it is especially important to note any potential reporting differences between the laboratories.

On the other hand, CAMI is interested in reporting all substances, at any detectable concentration, that may indicate performance impairment or a pre-existing medical condition, and which may have contributed to an accident. CAMI has a direct mandate to perform research on data that is discovered in this process. CAMI also endeavors to identify trends in drug usage by pilots, to improve testing procedures, or to help inform the FAA on policies that can increase aviation safety.

Another reason for the differences in drugs reported may be that the two laboratories tested different sample types. For example, the external laboratories may perform testing on a blood sample, while CAMI received only tissues for analysis. Finally, the differences reflected in Table 1 may be the result of differences in methods utilized for toxicology testing. Due to CAMI's mission, toxicology investigations may include a greater variety of drugs, such as antihypertensive and/or anti-arrhythmia medications, many of which do not fall under the normal scope of a ME/Coroner's mission.

Group I: Impairing/Controlled

The Impairing/Controlled Group consists of drugs that are known to cause impairment. Some of these, such as the selective serotonin reuptake inhibitors (SSRI drugs), are restricted by the FAA for pilot use, as discussed below. Other drug types in Group I include sedating antihistamines, opiates, cannabinoids, stimulants/sympathomimetics, benzodiazepines, cocaines, and volatiles.

Sedating antihistamines make up the drug type within Group I with the most frequently reported positive cases by both CAMI and the external laboratories. The sedating antihistamines in this study include diphenhydramine, cetirizine, doxylamine, chlorpheniramine, hydroxyzine, pheniramine, and promethazine. CAMI reported a sedating antihistamine in 125 cases, while the external laboratories reported these compounds in only 44 cases.

Although diphenhydramine (Benadryl, Sominex) is not a controlled substance, it is a drug noted to cause drowsiness, and pilots are cautioned about flying within a certain period after taking the

medication (6). In the current study, diphenhydramine is the most frequently reported drug for both CAMI (N= 70) and the external laboratories (N=34).

Cetirizine (Zyrtec) is traditionally considered a non-sedating antihistamine, but it has been demonstrated to produce a reduction in cognition for pilots (7). Cetirizine was the second most frequently reported sedating antihistamine by CAMI (N= 21) but external laboratories did not report it. This fact is likely due to cetirizine's reputation as a non-sedating compound. Other sedating antihistamines not reported by external laboratories include pheniramine and promethazine.

Opiates constitute the second most prevalent drug type reported by CAMI and the external laboratories. Opiates are critically impairing substances, and are receiving notoriety, with record numbers of people using these medications (8, 9). In decreasing order of frequency, opiates reported by CAMI included hydrocodone, dihydrocodeine, hydromorphone, tramadol, oxycodone, morphine, oxymorphone, buprenorphine, codeine, norbuprenorphine, o-desmethyltramadol, and methadone. It is significant that the external laboratories also reported at least one positive finding for each of the above opiate drugs.

The most commonly reported opiate was hydrocodone (Vicodin, Lortab) with CAMI reporting it in 20 cases, and the external laboratories reporting it 14 times. Overall, hydrocodone is the 82nd most highly prescribed medication in the United States (10). The second most often reported opiate for CAMI was dihydrocodeine. Dihydrocodeine is not only a parent drug, used for treating pain and cough but is also an active metabolite of hydrocodone. CAMI reported dihydrocodeine in 19 cases, while for external laboratories (N= 3). The third most reported opiate was hydromorphone. Hydromorphone is a parent drug used for treating pain, but it is also an active metabolite of hydrocodone. CAMI reported hydromorphone in 12 cases, for external laboratories (N= 3).

SSRIs made up the third most reported drug type for Group I. Four of these drugs, citalopram (Celexa), escitalopram (Lexapro), sertraline (Zoloft), and fluoxetine (Prozac), require a special issuance by the FAA for use, as mentioned above (11).

Citalopram is the most prevalent SSRI reported for both CAMI (N=19) and external laboratories (N= 11). CAMI also reported a high number of cases with the active metabolite, n-

desmethylcitalopram (N= 17), however, external laboratories did not report this drug. Additional active SSRI drugs and metabolites reported by CAMI included norsertraline, sertraline, fluoxetine, and norfluoxetine. CAMI reported 62 positive cases of parent drug and active metabolites from the combined analytical results of Celexa/Lexapro, Zoloft and Prozac. Therefore, the number of cases specifically reported from drugs requiring a special FAA issuance was approximately 2.8 times higher than that reported by the external laboratories.

Cannabinoids were the next drug type within Group I. Cannabinoids are compounds found within the marijuana plant. Δ^9-tetrahydrocannabinol (THC) is the primary psychoactive cannabinoid, and 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) is an inactive metabolite of THC. The CAMI laboratory found identical occurrence of both THC and THCCOOH (N= 28), while the external laboratories reported fewer cases for both parent drug (N= 14) and the metabolite (N= 9). The lower reporting frequency of THCCOOH for the external laboratories is probably related to the fact that this inactive metabolite does not play a role in determining the cause and manner of death. The higher reporting frequency of THCCOOH by CAMI is because the overall mission of the CAMI laboratory is to gain as much information as possible concerning prior drug use by a pilot.

Benzodiazepines are primarily used for their anxiolytic effects but are also known for their sedating properties and detrimental effects on psychomotor performance (12). The most commonly reported benzodiazepine for CAMI was lorazepam (N= 6), while the most commonly reported drug by external laboratories was nordiazepam (N= 4). Temazepam was reported by CAMI in three cases but was not reported by the external laboratories.

Cocaines comprise the drug type within Group I that is the least frequently encountered by CAMI. The CAMI laboratory reported cocaine and four metabolites: cocaethylene, benzoylecgonine (BE), anhydroecgonine methyl ester, and ecgonine methyl ester. The external laboratories reported cocaine and two metabolites, BE and cocaethylene. Levamisole is listed with cocaine as a related substance (RS) because it is commonly used as a cutting agent for cocaine. Levamisole was reported in two cases by CAMI but was not reported by the external laboratories. It appears that CAMI reported two fewer cases of cocaine, but when the metabolites are considered in all these cases, CAMI reported six cases with cocaine-related compounds and the external laboratories reported five cases.

Ethanol is the final drug listed in the Impairing/Controlled group. This compound is known to cause performance decrements and impair a person's ability to perform divided attention tasks, such as flying (13). Ethanol is the only substance that was reported in the same number of cases by both CAMI and external laboratories (N= 22). While ethanol represents the tenth most prevalent compound reported overall in CAMI cases, it ranked second in reporting by the external laboratories.

The high reporting frequency for ethanol, by both sets of laboratories, is related to the fact that this is the only drug that has legally mandated degrees of impairment associated with specific concentration values (4). Therefore, this is one of the most universally detected and reported substance for all forensic laboratories. All positive ethanol results in Table 1 are reported from cases in which the ethanol concentration, as reported by either CAMI or external laboratories, exceeds 40 mg/dL.

Group II: Routine OTC

The second group consists of common OTC medications that contain the following drug types: routine, nonsteroidal anti-inflammatory drugs (NSAID), antacids, and non-sedating antihistamines. The significant disparity in reporting between CAMI and the external laboratories for Group II is seen in Figure 2.

Salicylate, ibuprofen, acetaminophen, and naproxen were the most frequently reported Group II drugs by CAMI. They were also very frequently reported for the external laboratories. These drugs are commonly used for pain management or inflammation and may be purchased over-the-counter, thus probably explaining the high reporting frequency in cases.

The external laboratories do not report many of the other Group II drugs, such as oxymetazoline, fexofenadine, diclofenac, famotidine, loratadine, flufenamic acid, and guaifenesin. This is largely due to the fact that the medical examiner/coroner system, from which these cases come, are not concerned with the occurrence of routine OTC medications in regards to the cause and manner of death.

Group III: Cardio Active-Related

Group III, Cardio Active-Related compounds, constitutes a group of drugs that are commonly reported in CAMI cases (14). Group III also represents the largest difference between reporting

frequencies for CAMI and the external laboratories (Figure 2). CAMI reported 33 drugs in this group, while the external laboratories reported only seven. Metoprolol, a beta blocker, and amlodipine, a calcium channel blocker, were the top cardio-active drugs reported for both CAMI and the external laboratories. Metoprolol was also the most frequently reported beta blocker in a study analyzing the correspondence of reported drugs, and drugs actually found in CAMI cases (14).

Group IV: Rx Impairing

The fourth group, Rx Impairing, is important for aviation investigations because these compounds can cause issues with a pilot's ability to operate an aircraft. Drug types in this group include non-benzodiazepine anxiolytic/sedative compounds, antipsychotic compounds, vasodilators, tricyclic antidepressants, nerve pain treatments, muscle relaxants, atypical antidepressants, cognitive enhancement medications, drug abuse treatment medications, and anticonvulsants. The overall reporting frequency of Group IV for CAMI was about four times that of the external laboratories (Figure 2). Zolpidem (Ambien), a medication used for the treatment of insomnia, was the most frequently reported drug for CAMI (N= 18), and external laboratories (N= 6).

Group V: Other Drugs

The last group, Other Drugs, consists of drugs that do not readily fall into any of the four other groups, and include Emergency Medical Technician (EMT)/Hospital Medications, drugs for urinary retention, antibiotics, anti-diabetics, anti-inflammatory agents, acid reflux medications, antifungals, drugs for migraine headaches, and estrogen modulators.

While some of these drugs such as midazolam, alprazolam, fentanyl, ketamine, norketamine, propofol, and alpha-hydroxyalprazolam have potentially significant toxicological effects; their presence in this study is most likely attributed to treatment by an emergency medical technician (EMT) or by hospital personnel. Most of the remaining drugs reported in this group would be regarded as incidental findings by both CAMI and the external laboratories, and would not be considered as particularly relevant to a death investigation.

Two potentially notable exceptions could be the findings of anti-diabetic medications, and drugs for migraine headaches. The presence of these drugs could indicate the presence of a pre-existing medical condition that should have been captured in the pilot's DIWS records.

CAMI reported 90 positive cases from the analysis of 29 drugs, while external laboratories reported 35 cases from only ten drugs.

Drugs Most Frequently Reported by CAMI

The CAMI laboratory reported 166 different drugs during this five-year study. Twenty-six drugs were reported in 12 or more CAMI cases and were identified as a top drug for CAMI (Table 1). These drugs represent 57% of the total positives reported by CAMI but did not include any drugs from Group V (Other Drugs).

Seven of the top 26 drugs reported by CAMI came from the Cardio Active-Related group of drugs. Many of the pilots involved in fatal aviation accidents tend to be older subjects, and may often have cardiac issues. A previously cited reference (14), involving 319 pilot fatalities, noted that the average age of pilots taking beta blockers was 64 (SD= 10).

Drug usage for cardiovascular medical conditions is not only allowed but is required for continued medical certification of a pilot. Therefore, a part of CAMI's mission is demonstrating compliance with required medications, as listed on their DIWS records.

There were five drugs on CAMI's top list, which were not reported by the external laboratories. Three of these drugs were Cardioactive-related drugs, and the other two were cetirizine and n-desmethylcitalopram.

As previously discussed in the properties of Group 1 drugs, cetirizine has been demonstrated to produce a reduction in pilot cognition (7). It was also noted that citalopram is one of the drugs requiring FAA approval for use and that this was the most frequently reported SSRI for both CAMI and external laboratories. However, the active metabolite, n-desmethylcitalopram, was not reported by any of the external laboratories. Failure to report the presence of these two impairing drugs may potentially compromise the overall understanding of factors contributing to an accident.

Drugs Most Frequently Reported by External Laboratories

The external laboratories reported 82 different drugs. A drug reported in four or more cases was identified as a top drug for the external laboratories (Table 1). The external laboratories' top drug list included 28 drugs, which represents 72% of all drug-positive cases reported for these laboratories. The top drugs included drugs from all five groups, but only metoprolol and amlodipine were reported from the Cardio Active-Related Group. These particular Cardio-Active drugs were also listed on CAMI's top drug list.

For the great majority of drugs, CAMI reported more positive cases than the external laboratory; however, with two drugs, alprazolam and fentanyl, the external laboratories appeared to report a drug in more cases than CAMI. Both of these drugs are found in Group 5, under the drug type EMT/Hospital.

The external laboratories reported seven cases as positive for alprazolam, while CAMI reported it in only two cases. In four of these cases, CAMI received urine or tissue for analysis, while the external laboratories assayed blood samples. Decomposition was a significant factor in the tissue samples that were received for two cases. The CAMI laboratory detected benzodiazepines by immunoassay in each of these five "negative" cases; however, no benzodiazepine was confirmed by additional tests in the cases listed above.

With regard to fentanyl, the external labs reported the drug on six occasions, while CAMI reported the drug in only one case. Limited appropriate sample submitted to CAMI was a factor in each of these five "negative" instances.

The highest reported fentanyl concentration for external laboratories was 3.6 nanogram/milliliter (ng/ml), obtained in chest blood. In this case, we received only decomposed tissue. Fentanyl was not detected in our high-pressure liquid chromatography/mass spectrometry (hplc/ms) screening assays.

In a second case, the external lab analyzed antemortem blood, while the CAMI lab only received postmortem blood. In another case, the CAMI lab analyzed postmortem urine, while an external lab analyzed chest blood.

In a fourth case, both labs analyzed blood samples, and the external labs reported a value of 1 ng/ml, the lowest reported concentration by the external labs. While CAMI detected fentanyl in

an hplc/ms screening assay, the sample failed to confirm with additional confirmation tests on blood and muscle. While CAMI's limit of quantitation for fentanyl was 3 ng/ml, examination of the raw data indicated ion ratio failure for both samples analyzed.

In the final instance of apparent fentanyl discrepancy, the external laboratory did not actually submit autopsy results but used subpoenaed hospital records to indicate the presence of fentanyl.

As indicated above, CAMI did report a significant concentration of fentanyl in one case. While the highest concentration of fentanyl reported by external laboratories was 3.6 ng/ml in chest blood, CAMI reported a value of 148 ng/ml in blood and 89 ng/gram (ng/g) in liver. CAMI initially detected fentanyl in blood by using gas chromatography/mass spectrometry (gc/ms), and hplc/ms screening assays. Fentanyl was then confirmed and quantitated by gc/ms in blood and liver.

The external laboratories, however, reported a negative value for all analytes in this final "CAMI positive" case. Only immunoassay testing for cocaine and opiates was performed on the external sample, and this testing protocol will not detect fentanyl.

Quantitative Results

Two substances, ethanol and diphenhydramine, were selected to compare quantitative values obtained by CAMI and the external laboratories. These substances were found in a high frequency in this study, and quantitation was performed on blood samples analyzed by both CAMI and the external laboratories.

Table 2 examines the comparison of ethanol results between CAMI and external laboratories. A quantitative ethanol result in blood was available in 15 cases. Individual blood results for ethanol were compared on a case-by-case basis, with the percent difference determined for each of the two results. Any ethanol result greater than 40 mg/dL, whether reported by CAMI or the external laboratory, is included in the table. Overall, the mean for the 15 cases is quite comparable, with a value of 111 mg/dL and 122 mg/dL for CAMI and the external laboratories, respectively. Nine cases had a difference between paired samples of less than 20%, which is an accepted inter-laboratory variation for routine controls, as specified by the American Board of Forensic Toxicology (ABFT) (15).

In four of the remaining six ethanol cases, which demonstrated the highest percentage difference, cavity blood was the specimen tested by CAMI. The term "cavity blood" is usually given to a sample collected from a pool of blood present in the thoracic cavity due to severe internal injuries. This sample may be contaminated by fluids from other organs, including the stomach and liver. As a result, the ethanol content could differ significantly between a cavity blood sample and an intact heart, iliac vein, or femoral vein blood sample.

Table 3 examines the comparison of diphenhydramine results between CAMI and external laboratories. Seventeen cases had a quantitative diphenhydramine result in blood for both CAMI and the external laboratory. The mean for CAMI cases is 802 ng/mL and for the external laboratories' cases is 635 ng/mL. There was a wide variation in the results, with 10 cases having a percent difference greater than 20%. One explanation for this disparity might be the difference between the specimen type and/or the blood collection site, as discussed for ethanol. In many cases, CAMI tested cavity blood while the external laboratory tested blood from an intact heart or femoral vein. The values were in general agreement in those cases where each sample was known to come from an intact vessel.

Conclusions

This study is the first report to compare the results of toxicology testing performed at CAMI with those done by external laboratories investigating the same fatal aviation accidents. Cases in which there was both a CAMI report and an external laboratory report were compared. The original hypothesis, as previously stated in Methods, was that there would be no differences between these results. As determined in this study, however, this conjecture was proven to be incorrect.

Five groups of drugs were studied. Significant differences were found both in the number of different drugs detected and in the number of positive cases reported in each of the groups. The Impairing/Controlled category (Group I) was found to have the highest number of positive reports for both the CAMI and the external toxicology laboratories. This finding is a testament to the importance of detecting this drug group for the missions of both CAMI and the external laboratories. These drugs can cause death, or performance impairment, either alone, or in

combination with other substances. Therefore, these drugs may play a significant role in death investigations.

The high degree of overall correlation between CAMI and the external laboratories for Impairing/Controlled drug analysis, as seen in Figure 2, demonstrates that both CAMI and the external laboratories are detecting the impairing drugs quite well. This was especially significant in the demonstrated ability for external laboratories to detect at least one instance of every individual opiate detected by CAMI.

Another encouraging finding from this study was that the quantitative results for ethanol and diphenhydramine were in good general agreement, as seen in Tables (2, 3). This supports the fact that, despite differences in missions and methods, quantitative results will be similar between the laboratories considered in this study, and enhances the validity and interpretive value of each laboratory's work.

This study serves the forensic toxicology community by showing the potential relative variations that may occur between comparisons of postmortem laboratory results. Careful consideration has been given to the possible explanation for the marked differences in drug reporting between CAMI and the external laboratories. The most obvious explanation is that CAMI and the external laboratories have significantly different missions.

CAMI fulfills its mission in aviation safety research by providing information to FAA policymakers. CAMI also aids investigators, by detecting trace amounts of drugs in pilots involved in fatal aviation accidents. The detection of a greater number of drugs, and at a higher frequency than the external laboratories, shows that the focus of drug analysis at CAMI is concerned with issues that are of great concern to the aviation community, such as pilot incapacitation or impairment. This data is then used to determine the prevalence of drugs in the pilot population, to reveal usage trends that might suggest that more education is needed regarding drug effects on human performance, and to assist aviation medical examiners in making decisions regarding medical certification processes.

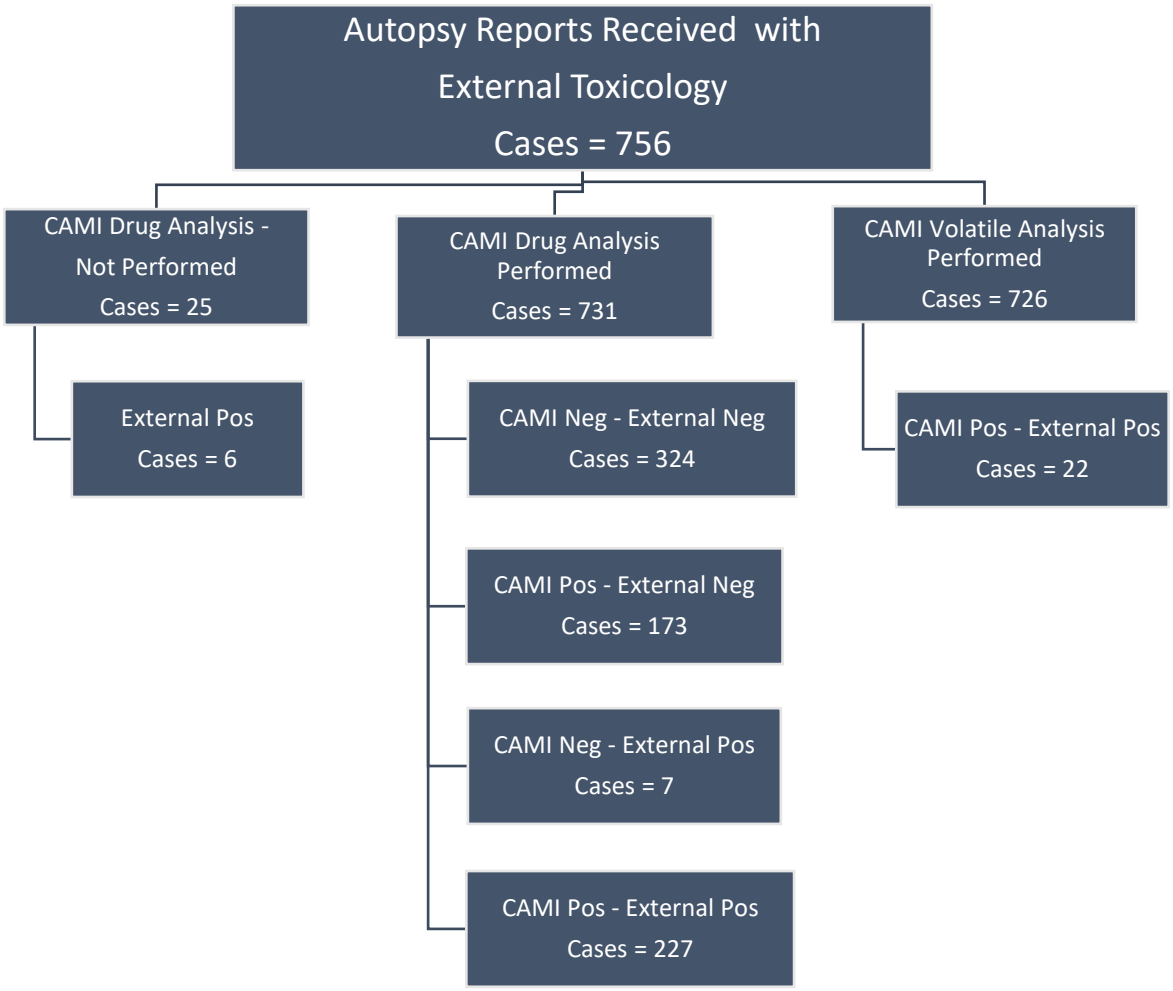

Figure 1. Flow Chart of Cases Received by CAMI with External Toxicology Results

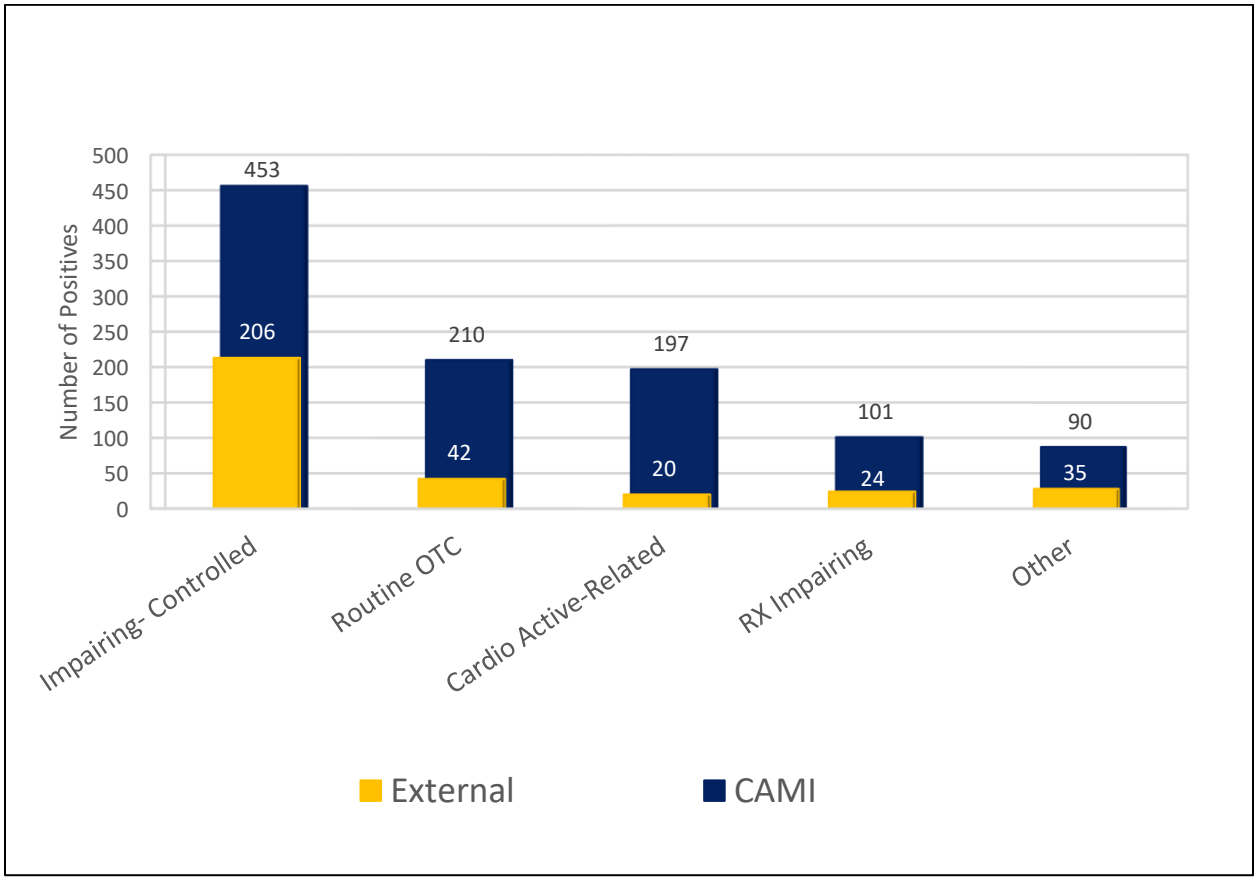

Figure 2. Number of Positives for Five Groups of Drugs Reported by CAMI and External Laboratories

Table 1. Drugs Detected by CAMI and the External Laboratories

Drug	Type	Group	CAMI	External
Diphenhydramine[1,2] (P)	Sedating Antihistamine	Impairing-Controlled	70	34
THC[1,2] (P)	Cannabinoids	Impairing-Controlled	28	14
THCCOOH[1,2] (IM)	Cannabinoids	Impairing-Controlled	28	9
Ethanol[1,2] (P)	Volatiles	Impairing-Controlled	22	22
Cetirizine[1] (P, AM)	Sedating Antihistamine	Impairing-Controlled	21	N/R
Hydrocodone[1,2] (P)	Opiates	Impairing-Controlled	20	14
Citalopram[1,2] (P)	SSRI/SNRI	Impairing-Controlled	19	11
Dihydrocodeine[1] (P, AM)	Opiates	Impairing-Controlled	19	3
N-desmethylcitalopram[1] (AM)	SSRI/SNRI	Impairing-Controlled	17	N/R
Doxylamine[1,2] (P)	Sedating Antihistamine	Impairing-Controlled	14	5
Hydromorphone[1] (P, AM)	Opiates	Impairing-Controlled	12	3
Pseudoephedrine[2] (P)	Stimulant/Sympathomimetic	Impairing-Controlled	11	6
Tramadol[2] (P)	Opiates	Impairing-Controlled	10	5
Chlorpheniramine[2] (P)	Sedating Antihistamine	Impairing-Controlled	9	4
Sertraline (P)	SSRI/SNRI	Impairing-Controlled	9	3
Desmethylsertraline (AM)	SSRI/SNRI	Impairing-Controlled	9	2
Ephedrine (P)	Stimulant/Sympathomimetic	Impairing-Controlled	8	N/R
Amphetamine[2] (P, AM)	Stimulant/Sympathomimetic	Impairing-Controlled	7	7
Oxycodone[2] (P)	Opiates	Impairing-Controlled	7	6
Hydroxyzine (P)	Sedating Antihistamine	Impairing-Controlled	7	1
Benzoylecgonine[2] (IM)	Cocaines	Impairing-Controlled	6	4
Morphine[2] (P, AM)	Opiates	Impairing-Controlled	6	4
Lorazepam (P)	Benzodiazepines	Impairing-Controlled	6	2
Anhydroec meth ester (IM)	Cocaines	Impairing-Controlled	6	N/R
Cocaine[2] (P)	Cocaines	Impairing-Controlled	3	5
Nordiazepam[2] (P, AM)	Benzodiazepines	Impairing-Controlled	5	4
Oxymorphone (P, AM)	Opiates	Impairing-Controlled	5	3
Ecgonine methyl ester (IM)	Cocaines	Impairing-Controlled	5	N/R
Methamphetamine[2] (P)	Stimulant/Sympathomimetic	Impairing-Controlled	3	4
7-amino-clonazepam (AM)	Benzodiazepines	Impairing-Controlled	4	3
Fluoxetine (P)	SSRI/SNRI	Impairing-Controlled	4	3

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Table 1. Drugs Detected by CAMI and the External Laboratories

Drug	Type	Group	CAMI	External
Norfluoxetine (AM)	SSRI/SNRI	Impairing-Controlled	4	3
Paroxetine (P)	SSRI/SNRI	Impairing-Controlled	4	2
Oxazepam (P, AM)	Benzodiazepines	Impairing-Controlled	4	1
Diazepam (P)	Benzodiazepines	Impairing-Controlled	3	3
Buprenorphine (P)	Opiates	Impairing-Controlled	3	2
Methylphenidate (P)	Stimulant/Sympathomimetic	Impairing-Controlled	3	2
Norbuprenorphine (AM)	Opiates	Impairing-Controlled	3	1
Temazepam (P, AM)	Benzodiazepines	Impairing-Controlled	3	N/R
Yohimbine (P)	Stimulant/Sympathomimetic	Impairing-Controlled	3	N/R
Codeine (P)	Opiates	Impairing-Controlled	2	3
Cocaethylene (AM)	Cocaines	Impairing-Controlled	2	2
O-desmethyltramadol (AM)	Opiates	Impairing-Controlled	2	1
Levamisole (RS)	Cocaines	Impairing-Controlled	2	N/R
Pheniramine (P)	Sedating Antihistamine	Impairing-Controlled	2	N/R
Phentermine (P)	Stimulant/Sympathomimetic	Impairing-Controlled	2	N/R
Promethazine (P)	Sedating Antihistamine	Impairing-Controlled	2	N/R
Chlordiazepoxide (P)	Benzodiazepines	Impairing-Controlled	1	1
Clonazepam (P)	Benzodiazepines	Impairing-Controlled	1	1
Duloxetine (P)	SSRI/SNRI	Impairing-Controlled	1	1
Methadone (P)	Opiates	Impairing-Controlled	1	1
Venlafaxine (P)	SSRI/SNRI	Impairing-Controlled	1	1
N-desmethyltramadol (IM)	Opiates	Impairing-Controlled	1	N/R
O-desmethylvenlafaxine (AM)	SSRI/SNRI	Impairing-Controlled	1	N/R
Di-N-desmethylcitalopram (IM)	SSRI/SNRI	Impairing-Controlled	1	N/R
Phenylpropanolamine (P)	Stimulant/Sympathomimetic	Impairing-Controlled	1	N/R
Salicylate[1] (P)	Routine OTC	Routine OTC	43	2
Ibuprofen[1,2] (P)	NSAID	Routine OTC	39	4
Acetaminophen[1,2] (P)	Routine OTC	Routine OTC	28	14
Naproxen[1,2] (P)	NSAID	Routine OTC	19	11
Ranitidine[1] (P)	Antacid	Routine OTC	16	2
Dextromethorphan[1,2] (P)	Routine OTC	Routine OTC	15	6
Dextrorphan[1] (AM)	Routine OTC	Routine OTC	12	1
Oxymetazoline (P)	Routine OTC	Routine OTC	10	N/R

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Table 1. Drugs Detected by CAMI and the External Laboratories

Drug	Type	Group	CAMI	External
Fexofenadine (P)	Nonsedating Antihistamine	Routine OTC	8	N/R
Diclofenac (P)	NSAID	Routine OTC	5	N/R
Quinine (P)	Routine OTC	Routine OTC	4	1
Famotidine (P)	Antacid	Routine OTC	4	N/R
Loratadine (P)	Nonsedating Antihistamine	Routine OTC	3	N/R
Desloratadine (P, AM)	Nonsedating Antihistamine	Routine OTC	2	1
Flufenamic acid (P)	NSAID	Routine OTC	1	N/R
Guaifenesin (P)	Routine OTC	Routine OTC	1	N/R
Metoprolol[1,2] (P)	Beta Blocker	Cardio Active-Related	29	7
Amlodipine[1,2] (P)	Ca Channel Blocker	Cardio Active-Related	26	6
Losartan[1] (P)	Angiotens Recept Blocker	Cardio Active-Related	23	N/R
Atorvastatin[1] (P)	Statin	Cardio Active-Related	18	1
Rosuvastatin[1] (P)	Statin	Cardio Active-Related	18	1
Valsartan[1] (P)	Angiotens Recept Blocker	Cardio Active-Related	16	N/R
Atenolol[1] (P)	Beta Blocker	Cardio Active-Related	12	N/R
Warfarin (P)	Anti-Coagulant	Cardio Active-Related	11	3
Carvedilol (P)	Beta Blocker	Cardio Active-Related	6	N/R
Triamterene (P)	Diuretic	Cardio Active-Related	4	N/R
Clonidine (P)	Anti-Hypertensive	Cardio Active-Related	3	N/R
Irbesartan (P)	Angiotens Recept Blocker	Cardio Active-Related	3	N/R
Telmisartan (P)	Angiotens Recept Blocker	Cardio Active-Related	3	N/R
Pravastatin (P)	Statin	Cardio Active-Related	2	1
Benazepril (P)	ACE Inhibitor	Cardio Active-Related	2	N/R
Clopidogrel (P)	Anti-Coagulant	Cardio Active-Related	2	N/R
Enalapril (P)	ACE Inhibitor	Cardio Active-Related	2	N/R
Propranolol (P)	Beta Blocker	Cardio Active-Related	2	N/R
Diltiazem (P)	Ca Channel Blocker	Cardio Active-Related	1	1
Bisoprolol (P)	Beta Blocker	Cardio Active-Related	1	N/R
Chlorthalidone (P)	Diuretic	Cardio Active-Related	1	N/R
Hydrochlorothiazide (P)	Diuretic	Cardio Active-Related	1	N/R
Labetalol (P)	Beta Blocker	Cardio Active-Related	1	N/R
Nadolol (P)	Beta Blocker	Cardio Active-Related	1	N/R
Norverapamil (AM)	Ca Channel Blocker	Cardio Active-Related	1	N/R
Quinapril (P)	ACE Inhibitor	Cardio Active-Related	1	N/R

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Table 1. Drugs Detected by CAMI and the External Laboratories

Drug	Type	Group	CAMI	External
Quinidine (P)	Anti-Arrhythmic	Cardio Active-Related	1	N/R
Ramipril (P)	ACE Inhibitor	Cardio Active-Related	1	N/R
Sotalol (P)	Beta Blocker	Cardio Active-Related	1	N/R
Ticlopidine (P)	Anti-Coagulant	Cardio Active-Related	1	N/R
Timolol (P)	Beta Blocker	Cardio Active-Related	1	N/R
Torsemide (P)	Diuretic	Cardio Active-Related	1	N/R
Verapamil (P)	Ca Channel Blocker	Cardio Active-Related	1	N/R
Zolpidem[1,2] (P)	Anxiolytic/Sedative	RX-Impairing	18	6
Azacyclonol (P)	Antipsychotic	RX-Impairing	8	N/R
Desmethylsildenafil (AM)	Vasodilator	RX-Impairing	7	N/R
Amitriptyline (P)	Tricyclic Antidepressant	RX-Impairing	5	1
Nortriptyline (P, AM)	Tricyclic Antidepressant	RX-Impairing	5	1
Sildenafil (P)	Vasodilator	RX-Impairing	5	N/R
Quetiapine (P)	Antipsychotic	RX-Impairing	4	2
Gabapentin (P)	Nerve Pain	RX-Impairing	4	1
Norcyclobenzaprine (IM)	Muscle Relaxant	RX-Impairing	4	N/R
Trazodone (P)	Anxiolytic/Sedative	RX-Impairing	4	N/R
Cyclobenzaprine (P)	Muscle Relaxant	RX-Impairing	3	2
Bupropion (P)	Atypical Antidepressant	RX-Impairing	3	1
Bupropion metabolite (AM)	Atypical Antidepressant	RX-Impairing	3	N/R
Doxepin (P)	Tricyclic Antidepressant	RX-Impairing	2	2
Meclizine (P)	Anxiolytic/Sedative	RX-Impairing	2	2
Nordoxepin (AM)	Tricyclic Antidepressant	RX-Impairing	2	1
Pramipexole (P)	Cognitive Enhance	RX-Impairing	2	1
Buspirone (P)	Anxiolytic/Sedative	RX-Impairing	2	N/R
Butalbital (P)	Anxiolytic/Sedative	RX-Impairing	2	N/R
Donepezil (P)	Cognitive Enhance	RX-Impairing	2	N/R
Minoxidil (P)	Vasodilator	RX-Impairing	2	N/R
Naltrexol (6-beta) (AM)	Drug Abuse Treatment	RX-Impairing	2	N/R
Carisoprodol (P)	Muscle Relaxant	RX-Impairing	1	1
Levetiracetam (P)	Anticonvulsant	RX-Impairing	1	1
Meprobamate (P, AM)	Anxiolytic/Sedative	RX-Impairing	1	1
Mirtazapine (P)	Atypical Antidepressant	RX-Impairing	1	1
Clomipramine (P)	Tricyclic Antidepressant	RX-Impairing	1	N/R
Clozapine (P)	Anxiolytic/Sedative	RX-Impairing	1	N/R

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Table 1. Drugs Detected by CAMI and the External Laboratories

Naltrexone (P)	Drug Abuse Treatment	RX-Impairing	1	N/R
N-desmethylclomipramine (AM)	Tricyclic Antidepressant	RX-Impairing	1	N/R
Valproic Acid (P)	Anticonvulsant	RX-Impairing	1	N/R
Vardenafil (P)	Vasodilator	RX-Impairing	1	N/R
Midazolam[2] (P)	EMT/Hospital	Other	11	8
Etomidate (P)	EMT/Hospital	Other	10	3
Alprazolam[2] (P)	EMT/Hospital	Other	2	7
Fentanyl[2] (P)	EMT/Hospital	Other	1	6
Lidocaine[2] (P)	EMT/Hospital	Other	6	4
Ketamine (P)	EMT/Hospital	Other	6	3
Tamsulosin (P)	Urinary Retention	Other	6	N/R
Trimethoprim (P)	Antibiotic	Other	5	1
Doxazosin (P)	Urinary Retention	Other	5	N/R
Norketamine (AM)	EMT/Hospital	Other	5	N/R
Atropine (P)	EMT/Hospital	Other	4	1
Terazosin (P)	Urinary Retention	Other	4	1
Alfuzosin (P)	Urinary Retention	Other	3	1
Pioglitazone (P)	Anti-Diabetic	Other	3	N/R
Sitagliptin (P)	Anti-Diabetic	Other	3	N/R
Colchicine (P)	Anti-inflammatory	Other	2	N/R
Propofol (P)	EMT/Hospital	Other	2	N/R
Alpha-hydroxyalprazolam (AM)	EMT/Hospital	Other	1	N/R
Atracurium (P)	EMT/Hospital	Other	1	N/R
Betazole (P)	Acid Reflux	Other	1	N/R
Fluconazole (P)	Antifungal	Other	1	N/R
Glipizide (P)	Anti-Diabetic	Other	1	N/R
Glyburide (P)	Anti-Diabetic	Other	1	N/R
Laudanosine (AM)	EMT/Hospital	Other	1	N/R
Montelukast (P)	Anti-inflammatory	Other	1	N/R
Ondansetron (P)	EMT/Hospital	Other	1	N/R
Rizatriptan (P)	Migraines	Other	1	N/R
Tamoxifen (P)	Estrogen Modulator	Other	1	N/R
Tolterodine (P)	Urinary Retention	Other	1	N/R

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Table 2. Ethanol Results by CAMI and External Laboratories, Concentration = mg/dL

	CAMI		External		
Case	**Specimen Type**	**Results**	**Specimen Type**	**Results**	**Percent Difference**
1	Femoral Blood	126	Femoral Blood	127	1%
2	Blood	154	Central Blood	160	4%
3	Blood	105	Cavity Blood	110	5%
4	Peripheral Blood	104	Blood	110	6%
5	Femoral Blood	153	Femoral Blood	163	6%
6	Blood	54	Blood	49	10%
7	Blood	161	Femoral Blood	180	11%
8	Blood	35	Cavity Blood	40	13%
9	Cavity Blood	247	Femoral Blood	291	16%
10	Heart Blood	172	Iliac Blood	217	23%
11	Cavity Blood	64	Blood	81	23%
12	Blood	105	Heart Blood	139	28%
13	Cavity Blood	67	Blood	118	55%
14	Cavity Blood	59	Left Chest Blood	30	65%
15	Cavity Blood	59	Left Chest Blood	20	99%
	Min	35		20	
	Median	105		118	
	Max	247		291	
	Mean	111		122	
	SD	56		72	

Table 3. Diphenhydramine Results by CAMI and External Laboratories, Concentration = ng/mL

	CAMI		External		
Case	**Specimen Type**	**Results**	**Specimen Type**	**Results**	**Percent Difference**
1	Heart Blood	1861	Heart Blood	1861	0%
2	Cavity Blood	64	Femoral blood	70	9%
3	Heart Blood	80	Peripheral Blood	90	12%
4	Blood	6852	Central Blood	6080	12%
5	Cavity Blood	69	Subclavian blood	78	12%
6	Iliac Blood	79	Blood	66	18%
7	Blood	109	Blood	87	23%
8	Cavity Blood	326	Chest Blood	220	39%
9	Cavity Blood	488	Chest blood	310	45%
10	Blood	329	Blood	520	45%
11	Blood	136	Blood	76	57%
12	Blood	56	Blood Femoral	110	65%
13	Blood	535	Heart Blood	272	65%
14	Cavity Blood	20	Femoral blood	50	87%
15	Cavity Blood	2171	Chest cavity	828	90%
16	Blood	432	Chest Blood	77	139%
17	Blood	32	Blood Peripheral	1	188%
	Min	20		1	
	Median	136		90	
	Max	6852		6078	
	Mean	802.3		635.1	
	SD	1680		1474	

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