



TOXTALK®

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PRESIDENT'S MESSAGE

Submitted by Ruth Winecker, Ph.D., F-ABFT



"Life's most persistent and urgent question is, 'What are you doing for others?'" Martin Luther King, Jr.

It's September, and as I sit here with the task of writing the last President's message before the Atlanta meeting, I find it difficult to come to terms with the fact that summer has flown by and the SOFT meeting is rapidly approaching. Where did the time go?

First, let me say that it means a great deal to serve as President at the annual meeting in my old home town. I was born about one mile from our meeting site, grew up in the Atlanta area and went to college 10 miles straight up Peachtree. Atlanta has a rich progressive history for those who choose to seek it out. In part, this is the reason I chose a quote by Martin Luther King, Jr. as my focus for this message. To me, being a toxicologist is the perfect answer to the question 'What are you doing for others?' My job allows me to serve the citizens of my state and provide answers to grieving loved ones, law enforcement and others who may be interested in what caused a particular death. Further, choosing to volunteer and serve in organizations such as SOFT, TIAFT and the AAFS help further the field of forensic toxicology. Helping others and serving a need, how cool is that?

As an organization, SOFT too, serves its members in many ways, including supporting committee activities and providing the membership with CE opportunities at the annual meeting. Please be sure to check out the latest meeting information in this issue. Robert Sears, Lisa Holt and their dedicated host of volunteers have been working hard all summer to bring

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PRESIDENT'S MESSAGE (CONTINUED)

you a fantastic meeting filled with learning opportunities, science and fun. I am looking forward to seeing you all there.

Recent committee activity includes work by SOFT's Committee for Long-Term Strategic Planning, which is reviewing and developing recommendations for the future growth of the organization. Chaired by Ted Shults, this important committee will be able to report to the membership at the 2015 Annual Meeting. Other highlights of the business meeting will be reports from all of SOFT's committees as well as recognition of members who have demonstrated longevity as a member of SOFT. This practice of recognizing SOFT members with 20 or more years of membership was started at the 2013 meeting and I am looking forward to acknowledging those folks and their commitment to SOFT. As an added bonus, the ribbon denoting number of years of membership (20, 30, 40 etc.) makes it easy for YFS and new members to spot potential mentors. So don't be shy, this is SOFT after all(!), go ahead and introduce yourself to a long time SOFT member. I'm sure you will make a new friend and valuable contact in the process. Don't forget about the raffle for a free meeting registration that is open to voting members who attend the business meeting. Therefore, please plan on attending the business meeting so that you can be updated on all the latest information, participate in planning for SOFT's future and possibly win a prize!

In keeping with tradition, the SOFT/JAT special issue of the *Journal of Analytical Toxicology*

will soon be available. It has been 35 years since the first JAT SOFT special issue was published and it remains a very special collaboration of SOFT members as special editor, authors and reviewers dedicated to producing an issue exclusive to the practice of forensic toxicology. Inside you will find topics related to new drugs, DUID, and postmortem toxicology which will benefit the entire membership of SOFT. Dr. Sumandeep Rana (Guest Editor) and her team of reviewers, as well as submitting authors, have done an outstanding job in helping to create this special publication.

In closing, I would like to say that SOFT members have a long history of service to the field and the community. A case in point is toxicologist, Elmer Gordon. (He believed that everyone could, and should, contribute, and as such the open forum is aptly named after him. As a young person starting out in the field of forensic toxicology, that means that you have opportunities to ask questions, offer answers and volunteer to serve. I hope that you do.



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The *Journal of Analytical Toxicology* is actively soliciting comprehensive review articles in the following areas:

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Nominating Committee Offers 2016 Slate of Officers

The **Nominating Committee's** task is to provide a slate of Officers and Directors to the full membership of SOFT at least 30 days prior to the annual Business Meeting, to be held in Atlanta, October 22, 2015.

The President and Vice President each serve one year terms, while the Secretary and Treasurer serve two year terms which expire in alternate years. Five additional Directors are elected for a three year term. If a Director cannot serve his/her entire term, an interim Director shall be named by the Board to serve the remaining term.

The 2015 SOFT Nominating Committee comprised of Michelle Peace, Dan Isenschmid, and Chair, Peter Stout respectfully submitted the following slate of Officer Nominations for consideration by the membership.

President

Jennifer Limoges, M.S., DABC

Vice President

Bruce Goldberger, Ph.D., F-ABFT

Secretary (2 year term)

Dwain Fuller, B.S., F-ABFT,
TC-NRCC

Director (3 year term)

Robert Sears, M.S., F-ABFT

Director (2 year term)

Amy Miles, B.S.



**Jennifer Limoges,
M.S., DABC**

**President
(one year term)**

Jennifer Limoges received her B.S. in Chemistry from Clarkson University and her M.S. in Forensic Science from the University of New Haven. She began working for the New York State Police as a Forensic Scientist in 1994. Currently, she is the Associate Director of Forensic Science for the Toxicology and Breath Testing departments of the NYSP Forensic Laboratory System. Ms. Limoges is an active member of the Society of Forensic Toxicologists (SOFT) and the American Academy of Forensic Sciences (AAFS). She has been a member of the SOFT Board of Directors since 2011 and currently serves as the Vice President. She is a member and past Chair of the SOFT/AAFS Drugs & Driving Committee, and has served on the SOFT Continuing Education Committee. She is a member and Past President of the Northeastern Association of Forensic Scientists (NEAFS), a member of the International Association for Chemical Testing (IACT), and a Diplomate of the American Board of Criminalistics (ABC). Ms. Limoges sits on the National Safety Council's Alcohol, Drug, and Impairment Division, and currently serves on their Executive Committee. She served as the Guest Editor for the 2009 SOFT Special Issue of the Journal of Analytical Toxicology (JAT).

Ms. Limoges' primary area of expertise is in impaired driving issues. She co-authored the 2013 JAT

publication "Recommendations for Toxicological Investigation of Drug Impaired Driving and Motor Vehicle Fatalities." She works regularly with the New York Prosecutors Training Institute (NYPTI), the New York Governor's Traffic Safety Committee, and Drug Recognition Experts on traffic safety matters. Ms. Limoges is a strong proponent of continuing education. She has hosted numerous workshops over the years at both the local and national level, providing training to toxicologists, law enforcement officers, and attorneys.

Ms. Limoges is also very active in standards development within the forensic science community. She is currently working on the AAFS initiative to become an accredited Standards Development Organization. She is a current member of the NIST Organization of Scientific Area Committees Toxicology Subcommittee, a past member of the Scientific Working Group for Forensic Toxicology (SWGTOX), and a past member of the National Commission on Forensic Science Subcommittee on Accreditation and Proficiency Testing.



**Bruce Goldberger,
Ph.D., F-ABFT**

**Vice President
(one year term)**

Dr. Bruce Goldberger is a Professor and the Chief of the Division of Forensic Medicine in the Department of Pathology, Immunology and Laboratory Medicine in the College of Medicine at the University of Florida in Gainesville, Florida. Dr. Goldberger is also the

Nominating Committee Offers 2016 Slate of Officers *(CONTINUED)*

Medical Director of UF Health Pathology Laboratories Clinical Toxicology Laboratory and the Director of the UF Racing Laboratory. Dr. Goldberger holds a joint Professor position in the Department of Psychiatry Division of Addiction Medicine in the College of Medicine and is the Director of the William R. Maples Center for Forensic Medicine and Program Director of the Florida Emergency Mortuary Operations Response System.

Dr. Goldberger received a Bachelor of Arts Degree in Zoology from Drew University in Madison, New Jersey and Master of Science and Doctor of Philosophy Degrees in Forensic Toxicology from the University of Maryland School of Medicine in Baltimore, Maryland. Dr. Goldberger is a Fellow of the American Board of Forensic Toxicology.

Dr. Goldberger is the editor-in-chief of the Journal of Analytical Toxicology. Dr. Goldberger is a past-President of the American Academy of Forensic Sciences, the President of the American Board of Forensic Toxicology, the Secretary of the Society of Forensic Toxicologists, and the Treasurer of the Forensic Specialties Accreditation Board.

Dr. Goldberger is the Technical and Administrative Director of the Forensic Toxicology Laboratory at the University of Florida which provides toxicological services to Medical Examiner Offices and State and local law enforcement agencies throughout the State of Florida. Dr. Goldberger has been qualified as an expert witness

more than 280 times in forensic toxicology in Federal, State, Military and Canadian courts of law.

Dr. Goldberger has published numerous articles related to forensic toxicology and is co-editor of the Handbook of Workplace Drug Testing, 1st and 2nd editions, On-Site Drug Testing and Garriott's Medicolegal Aspects of Alcohol, 6th Edition. Dr. Goldberger's studies in forensic toxicology have included the analysis of alcohol in breath and the measurement of therapeutic, abused and emerging drugs in biological tissues.

In recognition of his research achievements in forensic toxicology, Dr. Goldberger was presented with the first annual Sunshine Award from the Toxicology Section of the American Academy of Forensic Sciences in 1988. In addition, he was the 1994 recipient of the American Association for Clinical Chemistry's Outstanding Scientific Achievements by a Young Investigator Award. In 2004, Dr. Goldberger was the recipient of The International Association of Forensic Toxicologists' mid-career achievement award for excellence in forensic toxicology. Dr. Goldberger also received the Alexander O. Gettler Award in recognition of his outstanding contributions to the field and profession of forensic toxicology from the Toxicology Section of the American Academy of Forensic Sciences in 2006, the Outstanding Achievement Award from the Florida Association of Medical Examiners in 2008, and the Achievement in the Sciences Award from Drew University in 2012.



**Dwain Fuller, B.S.,
F-ABFT, TC-NRCC**

**Secretary
(two year term)**

Dwain Fuller holds a Bachelor of Science degree in Chemistry from the University of Oklahoma and serves as the Technical Director of the Toxicology and Clinical Mass Spectrometry Laboratories at the Veteran's Affairs North Texas Health Care Center in Dallas, Texas. Additionally, Mr. Fuller maintains an active private forensic toxicology consulting practice.

Mr. Fuller is certified as a Fellow of the American Board of Forensic Toxicology (ABFT) and as a Toxicological Chemist by the National Registry of Certified Chemists (NRCC). He is a Fellow of the American Academy of Forensic Sciences (AAFS) and a member of Southwestern Association of Toxicologists (SAT), in addition to being a member of SOFT since 1991. He is currently the Editor of ToxTalk® and serves on the SOFT Editorial Board for the Journal of Analytical Toxicology. Mr. Fuller previously served on the SOFT Board of Directors from 2008 to 2010. He has served on the Committee for Testing for Intoxication for the State of Nevada and as a panel member on the Governor's Conference on Safety for the State of Nevada. He has served on the faculty of the University of Texas Southwestern Medical Center at Dallas, the Texas Municipal Courts Education Center, and the National Judicial

Nominating Committee Offers 2016 Slate of Officers *(CONTINUED)*

College in Reno, Nevada. Mr. Fuller has served as the Chair of the Toxicology Section of the American Academy of Forensic Sciences and as a member of the Document Development Committee on Toxicology and Drug Testing in the Clinical Laboratory for the Clinical and Laboratory Standards Institute (CLSI).

Mr. Fuller began his career in forensic toxicology in 1984 at the Office of the Chief Medical Examiner for the State of Oklahoma. In 1987, he moved to Reno, Nevada to accept a position as the Assistant Director of Toxicology with Sierra Nevada Laboratories, Inc., a private laboratory which provided forensic toxicology services primarily to Northern Nevada law enforcement and coroner's offices. Mr. Fuller assisted in bringing Sierra Nevada Laboratories, Inc. to SAMHSA certification. Through a series of corporate purchases and mergers, Sierra Nevada Laboratories, Inc. became a Laboratory Corporation of America laboratory. In 1993, Mr. Fuller was promoted to the Director of Toxicology, and became the Responsible Person (RP) for the SAMHSA lab, positions he held until accepting his present assignment in 1998.

Mr. Fuller has chaired, co-chaired, and lectured at several workshops at the annual meetings of both SOFT and AAFS, and has authored or co-authored numerous papers and articles for both peer-reviewed and popular publications.



**Robert Sears, M.S.,
F-ABFT**

**Director
(three year term)**

Robert M. Sears is the Toxicology Technical Leader for the South Carolina Law Enforcement Division (SLED) in Columbia, South Carolina. He has been employed by SLED as a forensic toxicologist since 1988. Robert's responsibilities include analysis of biological specimens for alcohols, drugs and poisons and interpretation of associated findings in death investigation, sexual assault and driving under the influence cases. In addition, he provides new employee training, assistance in method development and validation, and instrument maintenance and troubleshooting.

Early in his career, Robert was involved in the development and support of SLED's laboratory information management system (LIMS) and associated reporting packages. For more than twenty years, he has been involved in the programming, implementation and support of various laboratory automation systems used for automated extractions of drugs and poisons from biological samples, to include Zymark/Caliper, Bio Integrated Solutions, Gilson and ITSP robotics systems.

Robert received the Bachelor of Science degree in Chemistry from

Francis Marion College in Florence, South Carolina and the Master of Science degree in Medicinal Chemistry from the University Of South Carolina College Of Pharmacy, Columbia, South Carolina.

Robert is a Fellow of the American Board of Forensic Toxicology (F-ABFT) and has been a board certified toxicologist since 1995. He currently serves as Secretary of the ABFT. Robert is a Fellow of the American Academy of Forensic Sciences, Full Member of the Society of Forensic Toxicologists and The International Association of Forensic Toxicologists, a regular member of the Southern Association of Forensic Scientists and the American Chemical Society. He was recently selected to serve on the National Institute of Standards and Technology - Organization of Scientific Action Committees Toxicology subcommittee. Robert has served as an on-site evaluator for the Forensic Science Education Programs Accreditation Commission (FEPAC) since 2008 and as a laboratory inspector for the National Laboratory Certification Program (NLCP) since 2009.

Robert has presented at local, regional and national scientific meetings and training events on topics related to solid phase extraction, method development and troubleshooting, automated extractions, and other topics related to forensic toxicology.

Nominating Committee Offers 2016 Slate of Officers *(CONTINUED)*



Amy Miles, B.S.

**Director
(two year term)**

Amy Miles is the Director of the Forensic Toxicology Program at the Wisconsin State Laboratory of Hygiene (WSLH). In addition to managing the Forensic Toxicology Program, Amy provides expert court testimony and interpretation of laboratory reports for coroners, medical examiners, attorneys and law enforcement officers. Amy also provides expert consultation for drug impaired driving cases both

locally and nationally. Amy attended the Drug Recognition Expert (DRE) school held in Wisconsin in 2004 and provides training and support for the DRE program. In 2005 Amy received an award from Citizens Against Drug Impaired Drivers (CANDID) for her outstanding dedication to the DRE program. Amy is the toxicology representative on the IACP DRE Technical Advisory Panel.

Amy has given numerous presentations on the topic of drugs, alcohol and human performance at state and national conferences and in-service trainings and has contributed several newsletter articles to

national publications. Amy is a faculty member of the Indiana University Robert F. Borkenstein Course: The Effects of Drugs on Human Performance. Amy has been appointed by the Illinois Supreme Court as a Guest Faculty member of the Illinois Judicial Conference Committee on Education. Amy is a member of several professional organizations and committees that pertain to alcohol, drugs and human performance and is the Chair of the SOFT/AAFS Drugs and Driving Committee. In 2010 and 2011 Amy was given the "Speaker of the Year" Award by the American Association for Clinical Chemistry.

Discounted Educational Opportunity for SOFT Members

SOFT has agreed to be a co-sponsor with ACMT for this upcoming educational event. As such SOFT members are eligible for the ACMT discount registration rate.

ACMT Seminars in Forensic Toxicology: A Legal "PotPourri"

December 9-10, 2015, Marriott City Center, Denver, CO

Day 1: The New World of "Legal Marijuana"

Day 2: Challenges in Toxicologic Consulting

Come and enjoy a specially crafted two-day conference that covers a pair of relevant and timely forensic topics. Day one is devoted to a spectrum of legal concepts focused on the medicinal and recreational use of cannabis. As marijuana expands into the fabric of everyday society, new and complicated issues continue to arise. The second day changes direction and addresses practical, real-world issues faced by any toxicologist with an active or burgeoning consulting practice. Again using seasoned experts, the conference will emphasize challenging, relevant issues such as the role of casual observers (aka. dram shop), postmortem toxicokinetics, and the subtleties of providing powerful testimony. Small group, interactive, and multimedia presentations will be used to enhance the curriculum. ACMT has had great success in developing educational programs for toxicologists of all backgrounds, including analytical, clinical, forensic, and medical toxicology.

For registration go to:

[http://www.acmt.net/2015 ACMT Seminars In Forensic Toxicology.html](http://www.acmt.net/2015%20ACMT%20Seminars%20In%20Forensic%20Toxicology.html)

CASE NOTES

Send interesting "Case Notes" to Section Editor

Matthew Barnhill, Ph.D., DABFT

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An Initial Look at Ketamine and Norketamine: Levels in a Pain Management Population

Submitted by Christopher Mitchell, Erin C. Strickland, Jeff Enders, Ian Shapiro, Christy Payne and Gregory McIntire

Ameritox, Ltd., Greensboro, NC

Ketamine is an arylcyclohexylamine derivative (Figure 1). It is classified as an NMDA (N-methyl-D-aspartate) receptor antagonist and is in the same class of drugs as phencyclidine (PCP). It was first developed in 1962 as a medication for starting and maintaining anesthesia and is sold in its salt form as Ketaset, Ketanest, and Ketalar. It isn't typically used as a primary anesthetic due to hallucinogenic effects hence, the observed illicit use. However, it is used in surgical and emergency situations either alone or in combination with low levels of opioids for its quick onset of action with minimal depressive effects on respiratory and cardiovascular performance. Medically, it is administered intravenously with a half-life of about 2.5 hours (Li, et al, Substance Abuse and Rehabilitation, 2011, 2; 11-20). Illicitly it is inhaled or orally ingested in a pure powder form or injected. Due to the rise in illicit activities, it became a Schedule III Control Substance in 1999. More recently, reports of ketamine treatment for post-traumatic stress disorder (PTSD) have begun to appear suggesting that prescription use of ketamine may increase

(e.g., Feder, et al., JAMA Psychiatry, 2014;71(6);681-688). With that in mind, we began to monitor pain patient urine samples for ketamine and norketamine to determine 1) frequency of positive samples and 2) absolute levels seen in this population. The data herein represent approximately 20,000 samples tested.

Ketamine undergoes metabolism in the liver where biotransformation alters it into norketamine initially and then dehydronorketamine. While norketamine is the major metabolite of ketamine, dehydronorketamine is reported to be the most prevalent metabolite detected in urine (Cheng, et. al., J.Chromatogr B Analyt Technol Biomed Life Sci 2007, 852(1-2), 443-449). Roughly 90% of ketamine has been reported to be excreted in urine with about 2 to 4% as the unchanged drug (Baselt, 10th ed.).

The analysis of ketamine and norketamine reported herein was completed using Agilent 1290 UP-LC/6460 MSMS systems as part of an overall illicit drug test method. The method was validated as per CAP requirements with a lower limit

of quantitation of 25 ng/mL for both analytes. Hydrolysis of several patient positive samples was attempted with negative results; i.e., there was no change from the initial results for ketamine or norketamine. Samples were not pretreated other than adding internal standard and centrifugation before injection directly onto the LC/MSMS.

Our analyses of ketamine and norketamine in urine drug samples from a pain management population over a two week period suggest that while not very prevalent in these samples, the composition of and the relative levels of ketamine and norketamine suggest at least some level of usage in this population (Table 1). In addition, our limited data indicate that dehydronorketamine is the more prevalent metabolite observed in the urine over norketamine consistent with reports in the literature (Baselt, 10th ed.).

The samples in Table 1 are all "positive" as per our validated cutoff of 25 ng/mL. Those few results less than 25 ng/mL were coupled with corresponding results of >25

An Initial Look at Ketamine and Norketamine: Levels in a Pain Management Population *(CONTINUED)*

Table 1. Levels of Ketamine, Norketamine and Dehydronorketamine in Pain Patients

Sample #	Ketamine (ng/mL)	Norketamine (ng/mL)	Dehydronorketamine (ng/mL)	Other Illicits (ng/mL)
1	14	28		
2	23	129		
3	31	29	82	
4	31	25		Amphetamine (>10,000)
5	33	32	201	
6	40	43		
7	45	34	108	
8	50	22		
9	80	38	1080	
10	150	58		
11	187	58	624	
12	191	112		Amphetamine (186)
13	237	187	1151	
14	357	255	571	
15	1759	>2500		

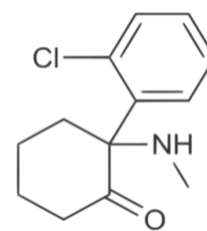
The method was validated to meet College of American Pathologists criteria. Reporting Cutoffs were 25 ng/mL for all analytes. Dehydronorketamine was not recorded for all samples.

ng/mL for the drug or metabolite, thus making the patient positive overall. None of these samples listed a ketamine drug in their medications. In the course of these studies, it was observed that some samples demonstrated a clear, observable peak at appropriate retention times (RT) with low background signal to noise (S/N) (i.e., a “clean” peak) for ketamine or norketamine albeit below the LOQ of the method. Finally, only 2 of these patients were positive for an additional illicit; in this case, amphetamine. In both cases, the patients were prescribed Adderall and thus the amphetamine use was not illicit. In those samples where dehydronorketa-

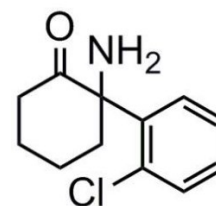
mine was monitored, it was always present at much higher levels than either ketamine or norketamine.

These initial data are consistent with a relatively low range of concentrations; certainly less than 500 ng/mL for most patients (singular exception noted above). The nature of the source of the ketamine detected is up for speculation since apparently none of these patients were prescribed the drug. Given that the concomitant use of illicit drugs is apparently low in this group, it is possible that these patients were under ketamine use for legal purposes.

Figure 1.



Ketamine



Norketamine

Tizanidine Intoxication in a Postmortem Case

Submitted by Ross J. Miller, M.D.¹, Brehon Davis, M.S.F.S, NRCC-TT²,
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Introduction

Tizanidine (Sirdalud, Ternelin, Zanaflex) is a synthetic, α_2 -adrenergic antagonist, imidazoline derivative that is used for short-term treatment of muscle spasticity (1,2). It is structurally similar to clonidine, but functions as a CNS muscle relaxant. Although the exact mechanism is not well established, it appears to have antagonistic effects on the α_2 -adrenergic receptors at the level of the spinal nerves (1,2). This drug-receptor interaction inhibits the activity of ventral (motor) neurons involved in the pain reflex. It is commonly prescribed for treating conditions associated with multiple sclerosis, amyotrophic lateral sclerosis, spastic diplegia, central nervous system and spinal trauma, and/or generalized back pain. Less commonly, it may also be prescribed as an anticonvulsant, as a sleep aide, and for treatment of fibromyalgia and headaches (migraine).

Tizanidine is supplied as an oral medication and formulated as a hydrochloride salt in tablet and capsule forms at doses of 2, 4, and 8 mg (3). The recommended dosage ranges between 2 to 8 mg three to four times a day. After ingestion, the entire drug is essentially metabolized in the liver via enzymes of the cytochrome P450 superfamily (CYP1A2) with an oral

bioavailability of 40% and a half life of 2 to 4 hours (3-6). The parent drug is broken into at least 7 inactive metabolites via oxidation; only 2% of the dose is eliminated unchanged in the urine and/or feces. Blood concentrations of tizanidine following therapeutic use generally do not exceed 0.025 mg/L.

Common adverse effects of tizanidine toxicity include dizziness, sedation, hallucinations, asthenia, dry mouth, blurred vision, bradycardia, and hypotension (3,7,8). Elevations in the serum liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are seen in approximately 5% of those taking this drug. These elevations are usually transient. However, rare reports of induced severe hepatotoxicity, subsequent acute liver failure and death have been reported (9). Deaths due to tizanidine overdose are extremely rare. We describe a death that resulted from tizanidine intoxication in combination with other drugs. We found only one published case report which describes death secondary to intentional overdose (10).

Case History

The decedent was an obese (body mass index = 42.8 kg/m²) 55 year old white female who was found unresponsive by her husband approximately 3 hours after she had

told him she was going to take a nap. Emergency personnel arrived and began resuscitation efforts that continued for approximately 40 minutes before she reached the hospital. Additionally, they recovered an empty bottle of tizanidine (90 pills to be taken once a day, prescribed 15 days prior) from the scene and brought it to the hospital. Soon after reaching the hospital, she was pronounced deceased. Investigation revealed that the decedent had a history of a gastric bypass surgery, diabetes, hypertension, fibromyalgia, bipolar disease, a "nervous breakdown" in 1995 and previous suicide attempts. More recently, the decedent's primary care provider reported that the decedent had been very depressed over the loss of a family member and had missed several appointments. Also noteworthy, family members indicated that the decedent usually slept in the nude. She had told them that if she were to do anything suicidal, she would be dressed when her body was found. She was clothed when her husband found her.

Results

The autopsy showed head and neck cyanosis. Contusions were identified on the left elbow, right abdomen, and right anterior neck. The neck contusion was associat-

Tizanidine Intoxication in a Postmortem Case (CONTINUED)

ed with a large hemorrhagic area (7 x 4 cm) involving the right sternocleidomastoid and omohyoid muscles. This injury was likely secondary to central line placement attempts in the emergency department. Internal examination revealed heavy lungs (right, 830 grams; left, 510 grams), splenomegaly (470 grams), and fractured ribs (anterior left 2nd and 3rd ribs). The rib fractures were likely secondary to cardiopulmonary resuscitation efforts. Apart from heart slides showing increased interstitial fibrosis, histological examination of multiple organs was unremarkable.

Postmortem heart blood, femoral blood, vitreous fluid, urine, gastric contents, brain tissue, and liver tissue were submitted for toxicological analysis. An enzyme multiplied immunoassay technique (EMIT) and liquid-liquid alkaline extraction followed by gas-chromatography/mass spectrometry (GC-MS) utilized femoral blood for a broad spectrum drug screen. Due to its inherent importance to this publication, it should be noted that tizanidine is not one of the drugs screened for in this assay. Gas-chromatography/flame ionization detection (GC-FID) and a Conway reagent were used to screen femoral blood for volatile compounds (ethanol, acetone, isopropanol, methanol).

While no volatile substances were detected, EMIT and GC-MS testing revealed the presence of doxepin, diphenhydramine, and diphenhydramine metabolite. Diphenhydramine was not quantified. A sample of femoral blood

was sent to an external laboratory for doxepin and tizanidine quantitation. Using liquid chromatography/tandem mass spectrometry (LC-MS/MS), tizanidine was measured at a concentration of 1.0 mg/L. Doxepin was determined to be present at 0.054 mg/L (reference range 0.05-0.150 mg/L) using gas chromatography.

Discussion

Common adverse effects associated with the use of tizanidine include dizziness, sedation, hallucinations, asthenia, dry mouth, blurred vision, bradycardia, and hypotension (2,7,8,11). Approximately 5% of those that use tizanidine will present with transient elevations in liver enzymes with significant complications. However, the hepatotoxicity rarely results in acute liver failure. Investigation of the decedent's medical history did not indicate symptoms of hepatotoxicity and gross and microscopic examination of the liver was unremarkable.

Deaths involving tizanidine seem extremely rare. Only one previously published case report described a situation in which death resulted from an intentional intoxication with this medication (10). This case described a 57 year old woman who was discovered unresponsive approximately 6 hours after being seen alive. At that time, she was noted to be intoxicated at a bar. She had a history of ethanol and prescription drug abuse. She also had a history of suicide attempts and a scene investigation found a suicide note near the body. Toxicological analysis of heart blood indicated toxic levels of tizanidine (2.3

mg/L) in combination with toxic levels of ethanol (0.16 g/dL) and diazepam (1.1 mg/L). The Medical Examiner ruled the cause of death as ethanol and combined drug intoxication, and the manner of death, suicide.

The case we present is similar to the previously published postmortem case in many ways. Both cases involved a middle aged female with a substance abuse history. Both women had a history of suicide attempts and both investigations found evidence which supported the manner of death as suicide. However, the toxicological profiles of both decedents differed. The level of tizanidine was higher in the published case (2.3 mg/L). Toxic levels of ethanol and diazepam were also present. The synergistic effect of these drugs when taken in combination would increase the decedent's risk for central nervous system depression, or decreased brain function, and the central regulation of breathing. The only toxic drug level in our case is the tizanidine, present at a concentration of 1.0 mg/L. Although not as high as the published case, it is still at a level well above the expected therapeutic maximum. Also, given that the source of blood was femoral (peripheral) and less likely affected by postmortem redistribution, the level measured here is likely more representative of the actual level at the time of death. The previously reported case measured tizanidine in heart blood. Doxepin was also quantified, but the level determined is not a toxic level by itself.

Tizanidine Intoxication in a Postmortem Case (CONTINUED)

Apart from obesity and evidence of circulatory and respiratory failure (cyanosis, congested organs), there was no other gross or microscopic evidence of disease or trauma that would explain her death. The autopsy findings in combination with the toxicological profile make our case unique because they suggest that tizanidine was the major contributor of death. The Medical Examiner ruled the cause of death as acute tizanidine intoxication and the manner of death, suicide.

Conclusion

Fatalities resulting from tizanidine overdose are very rare. To our knowledge, there is only one case currently reported in literature. Blood concentrations of tizanidine following therapeutic use generally do not exceed 0.025 mg/L. The decedent presented here has a tizanidine femoral blood level of 1.0 mg/L. Tizanidine was the only drug present at a toxic level in her tested samples and apart from obesity, there was no other contributing gross or microscopic factors leading to her death. This suggests that an overdose death from tizanidine can happen at a much lower concentration than that which has been previously published. Tizanidine is not detected by our GC/MS postmortem

drug screen, and thus the finding of an empty tizanidine prescription bottle at the decedent's house was critical in our death investigation. In its totality, this case indicates a death resulting from tizanidine toxicity and emphasizes the importance of a broad scoped death investigation when determining cause of death.

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SOFT Seeking Help!

HELP WANTED: in search of friendly people who enjoy meeting other friendly people. Must be in Atlanta during the SOFT conference (October 18-23, 2015) with an interest in all things toxic. Duties could include learning names at a workshop registration table; impersonating Vanna White with SOFT meeting signs; or starting a bidding war at the Silent Auction. If this sounds like your cup of poison, please click the link: <http://www.soft-tox.org/volunteers> and fill out the form to see how you can join the fun (better known as volunteering at the SOFT conference). We have a volunteer position to fit your schedule. No experience necessary.

Haldol® Analysis in Urine: The Impact of Beta-glucuronidase Hydrolysis

Submitted by Oneka Cummings, Ayodele A. Morris, Erin C. Strickland,
Jeffrey R. Enders, and Gregory McIntire

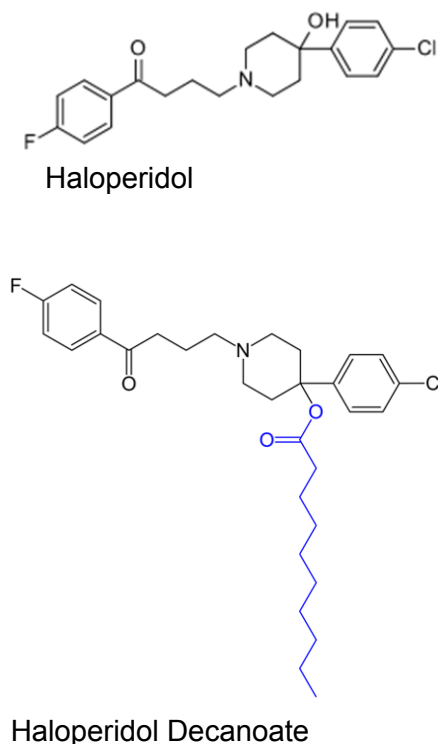
Ameritox, Ltd., Greensboro, NC

Haloperidol (Haldol®) is a typical antipsychotic prescribed for the treatment of acute symptoms of schizophrenia and many other mental health symptoms including Tourette syndrome and delirium. Potential drug adherence has been shown to be particularly low in patients with major depressive disorder (MDD) followed by bipolar disorder (BP) and less so in schizophrenia at 19% adherent (Millet, DeGeorge, et al.). A different report suggested that Haldol® patients are approximately 63.5% adherent overall regardless of disease as determined from patient samples with prescriptions (Millet, Ko, et al.). Urine drug testing has been employed by behavioral health clinicians to aid in monitoring patient compliance through analysis of drugs and their major metabolites (Cuoto, J.E., et al.). Typically, adherence to haloperidol therapy is monitored by evaluating levels of haloperidol and one or more metabolites found to be present in urine at approximately 2 and 4% of the total dose. In fact, unchanged Haldol® has been reported to be present in urine at less than 1% with no evidence of glucuronidation of the parent drug (Baselt, 10th ed.). These low levels of parent drug and/or metabolites after dosing increase the possibility of false negative monitoring results. Such false negative reports can improperly induce a clinician (e.g., a physician or psychiatrist) to alter a potentially compliant subject's Haldol® therapeutic regimen when alteration is unwarranted.

Haldol® has a molecular weight of 375.9 g/mol, a molecular formula

of C₂₁H₂₃ClFNO₂, pK_a of 8.3, log P of 3.66, CAS number of 52-86-8, and mass-to-charge ratio (m/z) of 376.5 when ionized with addition of a proton (via ESI MS). Haloperidol is commercially available as tablets (1, 2, 5, 10, or 20 mg), an oral solution (2 and 10 mg/mL), an injectable solution (5 mg/mL, max 20 mg/day), and as the injectable decanoate derivative (50 mg/mL).

Figure 1. Structures of Haloperidol and Haloperidol Decanoate



Interestingly, the structure of Haloperidol contains an -OH group that by analogy to the injectable decanoate version is reactive. Hence, we were curious as to whether this -OH group could be a site for glucuronidation as a metabolic step to remove drug from the

body. To this end, a series of studies were conducted with a beta-glucuronidase enzyme derived from recombinant technology (IMCSzyme®) to determine if concentrations of Haldol® increased or remained constant with hydrolysis. The use of this enzyme for any number of conjugated substrates was reported by Morris, et al. (JAT 2014).

Using an LC/MSMS method validated as per College of American Pathology criteria (Morris, et al. 2013), the effect of hydrolysis was studied on over 100 patient samples prescribed the medication. This method has an LOQ and reporting cutoff of 5 ng/mL for haloperidol. Results without hydrolysis and after hydrolysis at 65°C for 60 minutes are that for almost every sample the results are not just higher, they are substantially higher. It is difficult to calculate an average % increase in amount of Haldol® post-hydrolysis inasmuch as many samples that were “0” without hydrolysis increased dramatically (i.e., from negative to positive). Of course, there are patients who demonstrated a “0” without hydrolysis who remained “0” post-hydrolysis. These patients stand a good chance of not being adherent to their prescription.

These data are in direct contrast to reports in the literature (e.g., Baselt, 10th ed.) wherein conjugation of the parent drug “has not been reported”. Table 1 suggests that patient adherence is closer to 80% for those prescribed Haldol® than the earlier report of 63.5%.

Haldol[®] Analysis in Urine: The Impact of Beta-glucuronidase Hydrolysis (CONTINUED)

Table 1. Summary of Data: % Positive Results

Parameter	Without Hydrolysis	Post-Hydrolysis
Number of specimens	151	151
Minimum concentration (ng/mL)	0.0	0.0
Maximum concentration (ng/mL)	414.0	16805.6
Mean	30.7	982.5
Standard Deviation	66.7	1907.3
Total Positive	75	119
Total Negative	76	32
% Positive	49.67	78.81

These data were not separated by dose type. A small sample number of each dose type reveals the data in Table 2, wherein patients using the injectables (i.e., solution and decanoate derivative) are the most “adherent” as expected. Those on tablets are likely less adherent but still above the case where hydrolysis is not utilized. However, those patients taking the oral solution are likely extremely non-adherent. Again, this is from a small sample of data for various dosage forms of haloperidol following beta-glucuronidase hydrolysis to determine Haldol[®] levels in urine. A larger, more statistically significant data set may afford different results.

Table 2. Impact of Hydrolysis on % Positive Patients by Dosage Form

Dose type	Negative	Positive	% Positive	Failed SVT*
Injectable Haloperidol Decanoate	0/20	20/20	100%	2
Injectable Haloperidol Solution	3/35	32/35	94%	3
Haloperidol Tablets	26/181	155/181	85%	8
Haloperidol Oral Solution	73/106	33/106	31%	3

* Specimen Validity Testing (pH, specific gravity, and creatinine concentration)

Analysis of a different set of samples without hydrolysis (historical data) is shown in Table 3 and suggests that without hydrolysis, a significant number of “false negatives” are observed no matter what the dosage pathway. Obviously, suggesting that only 64% and 66% of patients who have been injected with drug are adherent leaves room to question the analytical method and hence the search for the glucuronide.

Table 3. % Positive Patients by Dosage Form without Hydrolysis

Dose type	Negative	Positive	% Positive	Failed SVT*
Injectable Haloperidol Decanoate	17/56	36/56	64%	3
Injectable Haloperidol Solution	59/178	119/178	66%	14
Haloperidol Tablets	284/646	362/646	56%	45
Haloperidol Oral Solution	N/A	N/A	N/A	N/A

Haldol® Analysis in Urine: The Impact of Beta-glucuronidase Hydrolysis

(CONTINUED)

Overall, these data demonstrate that hydrolysis before analysis of haloperidol in urine samples provides a greater level of sensitivity and consistency among subjects on Haldol® therapy, and therefore provides a superior urine analyte for evaluation of a subject's potential compliance with a Haldol® therapeutic regimen. Clearly, the presence of the glucuronidated form of haloperidol in urine is significant and represents an easier way to monitor potential adherence to this drug.

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TECHNICAL ARTICLES

Zolpidem and Driving – A Dangerous Mix

Submitted by Chuck Hayes, Regional Operations Coordinator
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Editor's Note: I came across an older version of this article while doing some research on a potential zolpidem driving case. I invited Mr. Hayes to update the article and submit it to ToxTalk®. He kindly obliged. I believe this to be useful information for SOFT membership. ~ DCF

It is a well-known fact that certain prescription drugs can impair driving ability. In a study using data

from the Fatality Analysis Reporting System (FARS), of motor vehicle crashes resulting in at least one fatality on U.S. roadways during 1993-2010, drivers tested for drug use accounted for 11.4 percent of all drivers involved in fatal crashes in 2010 (1). In addition, the recent U.S. Department of Transportation National Highway Traffic Safety Administration (NHTSA) report on the 2013-2014 national roadside survey on alcohol and drug use by drivers re-

vealed that approximately 22 percent of drivers tested positive for illegal, prescription, or over-the-counter drugs (2).

The results from both studies coincides with what many drug recognition experts (DREs), toxicologists, and other law enforcement officers are encountering in driving -under-the-influence (DUI) cases. An increased number of these cases involve impairing drugs other than alcohol, including legal prescription medications.

Zolpidem and Driving – A Dangerous Mix (CONTINUED)

One drug from the CNS depressant category having an impact on roadway safety is Zolpidem, available by prescription only and a Schedule IV controlled substance. It is typically available in strengths of 5 mg and 10 mg (white and pink oval tablets, respectively). This and other similar sleep-aide drugs are a non-benzodiazepine sedative-hypnotic used for short-term treatment of insomnia (3).

Zolpidem goes by a number of different brand names in the U.S. and abroad, with the most popular versions being Ambien®, Ambien CR®, Edluar®, Lunesta®, Intermezzo® and Zolpimist®. Each act on the GABAA receptor, resulting in central nervous system (CNS) depression. For this reason, users are cautioned to avoid operating heavy machinery or automobiles following administration. Driving impairment caused by Zolpidem is similar to that of ethanol and other CNS depressants. Adverse effects include blurred vision, thick slurred speech, and poor balance and coordination.

The issue of Zolpidem and driving became such a concern that impaired driving cases were studied in several states to learn more about its impact on traffic safety. In a State of Washington study, toxicologists identified 29 impaired cases between January 1997 and December 1999 where Zolpidem had been identified in the driver's blood. In five of the cases, Zolpidem was the only drug identified in the blood sample. The researchers concluded that it was reasonable to conclude that Zolpidem has the potential to affect driving in a negative way (4).

In another study with similar results, investigators attempted to determine the effect of middle-of-the-night administration of Zolpidem on driving ability. Thirty volunteers participated in a double-blind study to measure the effects of Zolpidem (10 or 20 mg) or a placebo four hours after administration. The subjects were tested for standard deviation of lateral position (drift). The authors concluded that a 10 mg dose of Zolpidem had a small effect while 20 mg significantly impaired driving (5).

To help better understand the effects of Zolpidem and driving, 27 actual impaired-driving cases involving the use of Zolpidem were reviewed using drug influence evaluation reports conducted by DREs. In each of the cases the suspect was unable to perform the Standardized Field Sobriety Tests (SFSTs) at roadside as instructed, was arrested for DUI, and referred to a DRE for further investigation. Each of the cases were examined to determine (1) cause of the stop and arrest, (2) performance on the DRE psychophysical tests, (3) results of the eye DRE examinations, including horizontal gaze nystagmus (HGN), vertical gaze nystagmus (VGN), lack of convergence (LOC), and (4) results of pulse rate (PR) and blood pressure (BP) checks.

In all 27 cases, blood samples were obtained and analyzed for the presence of drugs. In each of the cases alcohol was not detected and a full DRE drug evaluation was completed. In each case, according to the laboratory toxicology report, the only drug detected was Zolpidem. The Zolpidem blood concentrations

ranged from 0.05 to 0.69 mg/L with a mean of 0.22 mg/L.

Overview of the 27 Zolpidem DUI Cases

Case #1 involved a 35-year-old female driver involved in a crash. The subject had poor balance, and was slow to respond to questions. The Walk and Turn (W&T) and One Leg Stand (OLS) tests were stopped for safety reasons. Six clues of nystagmus (HGN) with an immediate angle of onset, and a Lack of Convergence (LOC) were detected. Her pulse rates (PR) and blood pressure (BP) were within the DRE average ranges. Toxicology confirmed 0.13 mg/L of Zolpidem.

Case #2 involved a 79-year-old male driver who crashed into another vehicle and then stuck a pedestrian. The subject was unsteady on his feet and unable to perform the DRE psychophysical tests, which were stopped for safety reasons. Six clues of HGN with an immediate angle of onset and LOC were detected. His PR and BP were above the DRE average ranges. Toxicology confirmed 0.14 mg/L of Zolpidem.

Case #3 involved a 46-year-old female driver detained for failing to maintain a single lane of travel. Her speech was slurred and she was disoriented. She performed poorly on the DRE psychophysical tests, exhibited six clues of HGN with an immediate angle of onset with LOC. Her PR and BP were above the DRE average ranges. Toxicology confirmed 0.15 mg/L of Zolpidem.

Zolpidem and Driving – A Dangerous Mix (CONTINUED)

Case #4 involved a 22-year-old female driver who collided in the back of another vehicle and attempted to leave the scene. Her speech was thick and slurred, and she was unsteady on her feet. She performed poorly on the DRE psychophysical tests and several were stopped for safety reasons. Six clues of HGN with an immediate angle of onset were observed along with Vertical Gaze Nystagmus (VGN) and LOC. Her PR were above the DRE average ranges and her BP was within the DRE average range. Toxicology confirmed 0.52 mg/L of Zolpidem.

Case #5 involved a 51-year-old female driver detained after being reported as a DUI. Her speech was thick and slurred. She performed poorly on the DRE psychophysical tests and several were stopped for safety reasons. Six clues of HGN with an immediate angle of onset were observed along with VGN and LOC. Her PR and BP were above the DRE average ranges. Toxicology confirmed 0.17 mg/L of Zolpidem.

Case #6 involved a 29-year-old male driver who collided with another vehicle. His speech was thick and slurred, and he was unsteady on his feet. He was unable to perform the DRE psychophysical tests. Four clues of HGN with LOC were detected. His PR was above the DRE average ranges and he refused to provide a BP. Toxicology confirmed 0.17 mg/L of Zolpidem.

Case #7 involved a 21-year-old male driver involved in a crash. His speech was thick and slurred, and he was unsteady on his feet. He performed poorly on the DRE

psychophysical tests and several were stopped for safety reasons. Six clues of HGN with an immediate angle of onset were detected along with VGN and LOC. His PR and BP were above the DRE average ranges. Toxicology confirmed 0.14 mg/L of Zolpidem.

Case #8 involved a 44-year-old female driver detained for failing to stop at a traffic light and then straddling the center line. Her speech was thick and slurred, and she was disoriented. She performed poorly on the DRE psychophysical tests. Six clues of HGN with an early angle of onset were detected along with VGN and LOC. Her PR and BP were within the DRE average ranges. Toxicology confirmed 0.26 mg/L of Zolpidem.

Case #9 involved a 65-year-old male driver involved in a crash. His speech was slow and slurred, and he was unsteady on his feet. The subject performed poorly on the DRE psychophysical tests and exhibited two clues of HGN with LOC. His PR were within the DRE average ranges and his BP was above the DRE average ranges. Toxicology confirmed 0.08 mg/L of Zolpidem.

Case #10 involved a 43-year-old female driver detained for failure to maintain a single lane of travel. Her speech was slow, thick and slurred. She performed poorly on the DRE psychophysical tests and several times nearly fell. She exhibited six clues of HGN with an immediate angle of onset, along with VGN and LOC. Her PR and BP were within the DRE average ranges. Toxicology confirmed 0.26 mg/L of Zolpidem.

Case #11 involved a 61-year-old male driver reported as a DUI who, before being stopped, hit a moped. His speech was slow, thick and raspy. He performed poorly on the DRE psychophysical tests. Six clues of HGN with an immediate angle of onset were detected along with VGN and LOC. His PR were at the low end of the DRE average ranges and his BP was within the DRE average range. Toxicology confirmed 0.32 mg/L of Zolpidem.

Case #12 involved a 39-year-old female driver who crashed into the concrete freeway barrier. Her speech was slow, low and raspy, and she was unsteady on her feet. She performed poorly on the DRE psychophysical tests, and exhibited four clues of HGN with LOC. Her PR were within the DRE average range and her BP was below the DRE average ranges. Toxicology confirmed 0.06 mg/L of Zolpidem.

Case #13 involved a 30-year-old female driver who hit a parked car. Her speech was slow and raspy, and she was unsteady on her feet. She performed poorly on the DRE psychophysical tests. Six clues of HGN, with an immediate angle of onset, and LOC were detected. Two of her PR were above the DRE average range and her BP was below the DRE average range. Toxicology confirmed 0.076 mg/L of Zolpidem.

Case #14 involved a 43-year-old male driver involved in a crash. His speech was slow and raspy, and he had poor balance and coordination. He performed poorly on the DRE psychophysical tests

Zolpidem and Driving – A Dangerous Mix (CONTINUED)

and exhibited four clues of HGN with LOC. His PR were above the DRE average ranges and his BP was within the DRE average ranges. Toxicology confirmed 0.05 mg/L of Zolpidem.

Case #15 involved a 53-year-old male who was driving slowly and stopping at green traffic lights. His speech was slow and raspy, and he was unsteady on his feet. He performed poorly on the DRE psychophysical tests and exhibited six clues of HGN with VGN and LOC. His PR and BP were all within the DRE average ranges. Toxicology confirmed 0.11 mg/L of Zolpidem.

Case #16 involved a 65-year-old female driver who drove over a curb and hit a parked car. Her speech was slow, thick and raspy, and she was unsteady on her feet. She performed poorly on the DRE psychophysical tests and nearly fell several times. Six clues of HGN with an early angle of onset were detected along with VGN and LOC. Her PR and BP were above the DRE average ranges. Toxicology confirmed 0.17 mg/L of Zolpidem.

Case #17 involved a 57-year-old male who was driving slowly and unable to maintain a single lane of travel. His speech was slow and slurred, and he had poor balance and coordination. He performed poorly on the DRE psychophysical tests and several were stopped for safety reasons. He exhibited four clues of HGN with LOC. His PR were within the DRE average ranges and his BP was at the low end of the DRE average ranges. Toxicology confirmed 0.06 mg/L of Zolpidem.

Case #18 involved a 35-year-old male driver reported as a DUI who drove over the curb when stopped. His speech was slow and slurred, and he had poor balance. He performed poorly on the DRE psychophysical tests and the W&T was stopped for safety reasons. Six clues of HGN along with VGN and LOC were detected. His BP was at the low end of the DRE average range. Toxicology confirmed 0.65 mg/L of Zolpidem.

Case #19 involved a 73-year-old female driver who collided with a parked car. Her speech was slow and slurred. She performed poorly on the DRE psychophysical tests and exhibited two clues of HGN with LOC. Her PR and BP were above the DRE average ranges. Toxicology confirmed 0.23 mg/L of Zolpidem.

Case #20 involved a 29-year-old female driver reported as a DUI stopping at green traffic lights and disobeying red lights. Her speech was slow and slurred, and she had poor balance and coordination. She performed poorly on the DRE psychophysical tests and exhibited six clues of HGN with an early angle of onset. VGN and LOC were also detected. Her PR were above the DRE average range and her BP was within the DRE average ranges. Toxicology confirmed the presence of Zolpidem but no quantitative level was reported.

Case #21 involved a 52-year-old female driver reported as a DUI driving over the center line. She was unsteady on her feet, performed poorly on the DRE psychophysical tests, and nearly fell attempting the W&T. She exhibited

six clues of HGN with LOC. Her PR were within the DRE average ranges and her BP was below the DRE average ranges. Toxicology confirmed 0.17 mg/L of Zolpidem.

Case #22 involved a 26-year-old male stopped for driving outside his lane and making a wide sweeping turn. His speech was thick and slurred, and he had poor balance and coordination. He performed poorly on the DRE psychophysical tests and nearly fell during the W&T and OLS. Six clues of HGN were detected along with VGN and LOC. His PR and BP were above the DRE average ranges. Toxicology confirmed 0.27 mg/L of Zolpidem.

Case #23 involved a 48-year-old female driver who failed to stop at a red light, crossed the center line, and then drove over the curb onto a lawn. Her balance and coordination were poor and she performed poorly on the DRE psychophysical tests. She nearly fell attempting the W&T. Six clues of HGN with LOC were detected. Her PR were within the DRE average ranges and her BP was above the DRE average range. Toxicology confirmed 0.27 mg/L of Zolpidem.

Case #24 involved a 47 year-old female driver that collided with a stopped vehicle. She performed poorly on the DRE psychophysical tests and exhibited six clues of HGN with LOC. Her PR and systolic BP was above the DRE average ranges. Toxicology confirmed 0.10 mg/L of Zolpidem.

Case #25 involved a 65-year-old male driver reported as a DUI who was weaving outside his lane and

Zolpidem and Driving – A Dangerous Mix (CONTINUED)

almost crashed. His speech was slow and slurred. He was unable to perform the DRE psychophysical tests, and exhibited four clues of HGN with LOC. His PR were at the high end of the DRE average range and his BP was within the DRE average ranges. Toxicology confirmed 0.69 mg/L of Zolpidem.

Case #26 involved a 42-year-old female driver reported as a DUI and unable to maintain a single lane of travel. Her speech was thick and slurred, and she had poor balance and coordination. She performed poorly on the DRE psychophysical tests and nearly fell several times. Six clues of HGN with VGN and LOC were detected. Her PR were within the DRE average ranges and her BP was below the DRE average range. Toxicology confirmed 0.19 mg/L of Zolpidem.

Case #27 involved a 35-year-old female driver involved in a crash. She was unable to perform the DRE psychophysical tests, which were stopped for safety reasons. Six clues of HGN with an immedi-

ate angle of onset were present along with LOC. Her PR were within the DRE average range and her BP was at the high end of the DRE average range. Toxicology confirmed 0.13 mg/L of Zolpidem.

The following chart represents information collected from the 27 Zolpidem cases in which the drivers were evaluated by a DRE. The information includes the cause of the stop/arrest, the subject's performance on the DRE psychophysical tests, results of the DRE eye examinations, (HGN, VGN, LOC), and the subject's pulse rates (PR) and blood pressure (BP).

Conclusion

Zolpidem and other similar hypnotics act as sleep inducers. The well-documented relationship between fatigue, sleepiness, and driving performance make Zolpidem and other similar hypnotics potentially hazardous to vehicle operation. Based upon past studies addressing Zolpidem and driving, and using the information collected from actual DRE Zolpidem-impaired driving

cases, it is reasonable to conclude that normal prescribed doses of Zolpidem and similar hypnotics do adversely affect driving. It is also reasonable to conclude that when law enforcement officers encounter persons suspected of driving under the influence of Zolpidem and other similar hypnotics, they may observe a variety of impairment indicators that may or may not follow the "classic" or traditional CNS depressant impairment signs and symptoms; however, some of the more common indicators appear to be horizontal gaze nystagmus (HGN) with an early angle of onset, lack of convergence (LOC), vertical gaze nystagmus (VGN) and poor performance on the psychophysical tests.

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27 DRE Zolpidem DUI Cases			
Subjects:	Male – 12	Female – 15	Age range: 21 – 73 (Mean: 45.7)
Stop/Arrest:	Crash – 13	Weaving – 7	Reported as DUI – 4 Other – 3
DRE Psychophysical Tests:	Stopped – 8	Completed with difficulty - 19	
HGN:	6 clues (max) – 19	4 clues – 6	2 clues – 2 Early/Immediate Onset - 13
Other Eye Indicators:	Vertical Gaze Nystagmus (VGN) – 12		Lack of Convergence (LOC) - 27
Pulse Rate:	Within DRE Range – 13	Above DRE Range – 14	Below DRE Range - 0
Blood Pressure:	Within DRE Range – 12	Above DRE Range – 11	Below DRE Range - 4
Zolpidem Toxicology Results:	Range – 0.05 to 0.65 (Mean – 0.24)		

Zolpidem and Driving – A Dangerous Mix (CONTINUED)

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3. Couper F, Logan B. *Drugs and Human Performance Fact Sheets*, NHTSA, April 2014, DOT HS 809 725.
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5. Verster, JC et. al. *Residual Effects of Middle-of-the-night Administration of Zaleplon and Zolpidem on Driving Ability, Memory Functions, and Psychomotor Performance*. J. Clin. Psychopharmacol., 2002, Dec: 22(6): 576-83

SOFT 2015 Atlanta Update

Submitted by Robert Sears and Lisa Holt



Happy (almost) fall, everyone!

The final stages of this year's 45th annual meeting of the Society of Forensic Toxicologists are underway and the preparations are almost complete. Our attendance this year is anticipated to be over 1000, and we are incredibly excited to have all of you joining us here in Atlanta!

Our workshops this year cover a wide range of topics, with something sure to please just about everyone. We are also introducing a SOFT 2015 app from Crowd Compass, so you will be able to keep up with all the latest schedules, speakers and activities throughout the week. This app includes maps of important meeting spaces, such as the event area itself, exhibitor locations, and the Tox 'N Purge fun run. There is also an up to date schedule of events, a listing of all the speakers, as well as our generous sponsors and exhibitors. If you're interested in checking the app out now, you can complete the free download at the app store for your mobile device (using the search title 'SOFT-TOX'). Enjoy!



Another item we are introducing this year is an Elmer Gordon Forum topic suggestion box. In an effort to facilitate conversation at the Elmer Gordon Forum, we will be soliciting suggested topics for discussion in advance. Be sure and look for the suggestion box at the registration desk, and don't hesitate to participate. We'd really enjoy hearing from you.

Because we are expecting such a great attendance this year, we are including some alternate hotel information on the SOFT-tox.org website to assist our guests with their arrangements, should that be needed. The SOFT website also has much more information on it to help your meeting be the best it can, including the most current information on schedules, the scientific program summary, as well as an online registration form (if you haven't registered yet, what are you waiting for? We'd love for you to join us!).

With only about one month left until the meeting, there is a flurry of activity as the hard working Planning Committee puts the final touches on a fantastic conference. After just a little more polish and shine before the company arrives, this meeting is certain to be one for the books.

We can't wait to see you there!

Lisa and Robert



FROM THE TOXICOLOGY LITERATURE

Submitted by Kevin G. Shanks, M.S., D-ABFT-FT

kshanks@aitlabs.com

AIT Laboratories, Indianapolis, IN

Clinical Toxicology (Philadelphia) June 2015

Volume 53, Issue 5 Loperamide Toxicokinetics: Serum Concentrations in the Overdose Setting

In this letter, Eggleston *et al.* reported a 30 year old male who presented to the hospital after abusing loperamide, the opioid substance found in Imodium anti-diarrheal medication. After leaving the hospital against physician's order, he was found unresponsive by a family member and was brought to the hospital again where multiple ventricular arrhythmias were documented, as well as ventricular tachycardia. He was defibrillated multiple times. The patient self-reported he chronically consumed two hundred 2 mg loperamide tablets every day for the last week. Serum samples were drawn after admission and a toxicokinetic profile of loperamide was constructed. The first two serum specimens demonstrated a loperamide half life similar to previously published studies (8.9 hours). But subsequent specimens demonstrated extended half lives of approximately 35 hours. Caveats to this data include the patient's health history (Crohn's disease, multiple bowel resections, ileostomy) and other concurrent medications including buprenorphine and amiodarone.

Journal of Analytical Toxicology July/August 2015 Volume 39, Issue 4 An Acute Acetyl Fentanyl

Fatality: A Case Report with Postmortem Concentrations

McIntyre *et al.* reported a death of a 23 year old man who had a history of drug abuse including heroin. A syringe with needle and rubber tourniquet was found in his bedroom closet. Findings at autopsy included three recent puncture wounds in the left forearm and antecubital fossa, pulmonary edema, and congestion. Microscopic examination found small amounts of foreign material in the lungs and left arm vein. No other findings were documented. Toxicological analyses revealed acetyl fentanyl in various specimens (peripheral blood, 260 ng/mL; central blood, 250 ng/mL; liver, 1000 ng/kg, vitreous humor, 240 ng/mL; urine, 2600 ng/mL). Cause and manner of death was certified as accidental acute acetyl fentanyl intoxication.

The New England Journal of Medicine July 2015 Volume 373

Synthetic Cannabinoid-Related Illnesses and Deaths

Trecki *et al.* discuss recent increase in reports of severe toxicity and deaths associated with synthetic cannabinoids in the USA. The authors list several recent cases in which synthetic cannabinoids have been involved, but discuss no case history or circumstances, pathological findings at autopsy, or even certified cause and manner of death. The specific synthetic cannabinoids included in the deaths are AB-CHMINACA, AB-PINACA,

ADB-PINACA, AM-2201, MAB-CHMINACA, and XLR11.

Drug Testing and Analysis July 2015

Volume 7, Issue 7 Morphine and Codeine in Oral Fluid after Controlled Poppy Seed Administration

Concheiro *et al.* reported a controlled dosing study in which they administered two 45 gram raw poppy seed doses (15.7 mg morphine/3.1 mg codeine) to 17 adults. Doses were consumed 8 hours apart. Oral fluid specimens were collected (n=459) throughout a 32 hour time range and analyzed by LC/MS/MS. Peak concentrations for morphine and codeine were 177 ng/mL and 32.6 ng/mL respectively. Time to peak concentrations for morphine and codeine were 0.5-1 hour and 0.5-2.5 hours respectively. After completed dosing, the windows of detection for the last positive morphine result was 1 hour (40 ng/mL) cutoff or 0.5 hour (95 ng/mL).

Journal of Analytical Toxicology September 2015

Volume 39, Issue 7 Ethylone-Related Deaths: Toxicological Findings

Lee *et al.* reported a series of nine fatalities related to the substituted cathinone, ethylone. All decedents were male. Age range was 18-32 years. Seven of the nine cases had blood ethylone concentrations ranging from 38 to 2,572 ng/mL. One case had blood ethylone concentration less than 25 ng/mL.

FROM THE TOXICOLOGY LITERATURE (CONTINUED)

One case had no detectable ethylone in the blood specimen. Other drugs detected in these fatalities included alprazolam, benzoylecgonine, diphenhydramine, ethanol, morphine, THC-COOH, and tramadol. Causes of death included gunshot wound, mixed drug intoxication, blunt force trauma, hanging, and undetermined.

Annals of Emergency Medicine
September 2015
Volume 66, Issue 3
Unintentional Pediatric Expo-

sure to a Synthetic Cannabinoid (AB-PINACA) Resulting in Coma and Intubation

Thornton *et al.* reports the case of a 10 month old female who chewed on a synthetic cannabinoid containing cigarette. She was taken to the emergency room by her mother within 30 minutes of being found. The female's pulse rate was 132 beats/minute. Her blood pressure was 106/69 mm Hg. Her respiratory rate was 34 breaths/minute. Normal mental status was documented.

Within 90 minutes, the child's response to verbal and physical stimuli stopped and she developed respiratory depression which required intubation. The child was admitted and tested positive for influenza A. The child was intubated for 36 hours but recovered fully. Toxicological analysis of the admission serum was positive for AB-PINACA (42 ng/mL) and AB-PINACA N-pentanoic acid (345 ng/mL). No other compounds were detected.

MATT Annual Meeting 2016

MATT Annual Meeting 2016

APRIL 14-15

CROWNE PLAZA DOWNTOWN

ST. LOUIS, MO

CALL FOR ABSTRACTS

PRESENTATIONS OR POSTERS



We are currently accepting abstracts for the 2016 Annual Meeting of the Midwest Association for Toxicology and Therapeutic Drug Monitoring. Please e-mail your title and abstract (200 words or less) to Michele Glinn (mglinn@etlab.org) by Feb 26, 2016.

Please include:

- Your name and any co-authors
- Organization Name
- E-mail address
- Postal address
- Phone Number
- For presentations, please indicate whether you prefer a 15 or 30 minute time slot and we will try to accommodate your request.

We will have a projector and laptop computer for your PowerPoint presentations. Once approved, please send presentation via e-mail to have it pre-loaded for the meeting. For posters, details will follow regarding times and location of poster session. Also, please let us know if we can share your slides with the group via thumb-drive and meeting notebook shared with attendees.

MORE INFORMATION TO FOLLOW

CHECK WWW.MIDWESTTOX.ORG FOR DETAILS

THANK YOU! SOFT 2015 Meeting Exhibitors and Sponsors

Note the long list of 82 companies that will join the SOFT 2015 Exhibitors at the Annual Meeting in October. They will be prepared to share the latest innovations and product advancements in laboratory instrumentation. Most of these exhibitors have partnered with SOFT for many consecutive years. The financial commitment from our exhibitors is essential in keeping meeting registration fees low for attendees.

Please acknowledge their collective generous contributions and extend your appreciation and business toward these indispensable associates. Those companies who have committed additional financial funding are showing in **BOLDED** print. Sponsorships provide for the social receptions, breakfasts, lunches, refreshments, and special events.

THANK YOU ALL!

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UCT, Inc.
UTAK Laboratories, Inc.
Waters Corporation
Wiley
X-Link Bioscience, Inc.



IN MEMORIAM

Francis Merrill (Fran) Urry



Dr. Francis Merrill Urry passed away Sunday July 12, 2015 with his family at his side. Dearly loved by family and friends, he lived a productive and honorable life. He was born August 23, 1937 to Francis Lester Urry and Virginia Leona Carroll at LDS Hospital in Salt Lake City, UT. Fran attended Bryant Junior and South High Schools before his family moved to Burbank, CA for a year where he attended Burbank High and played football and basketball. After returning to SLC he completed school at West High graduating in 1955. He attended the University of Utah, earned two degrees from the University of Florida, and attained a PhD in Toxicology at Utah State University. March 1960 Fran joined the Marine Reserves, training in San Diego with the Second Battalion Platoon 226. Upon graduation he was designated Platoon Honorman. He finished in the Marine Intelligence Corps based in Jacksonville, FL.

Fran married Judith Evelyn Tilton of Palatka, FL on September 15, 1961 in the LDS Salt Lake Temple. They are the parents of 6 children: Tamara Dale Urry (Kenneth Pattinson), James Tilton Urry (Jeanette Magleby), Dan Tilton Urry (Stephanie Knowles), Shannon Leigh Gracen (Michael Schmidt), and Joseph Tilton Urry; 16 grandchildren and four great-grandchildren. Also survived by sisters Grace Henderson (David), Jane Harris (Van), and Virginia Jensen (Rees). Preceded in death by parents and baby daughter, Linda Rae Urry. Fran enjoyed learning, physical activity, dogs, square dancing and his friends. He cherished his family and was kind with a subtle sense of humor.

Career: Faculty member of department of Pathology at the University of Texas Medical Branch, Galveston, TX; Utah State Public Health Laboratory Toxicologist for the State Medical Examiner and Director of the Laboratory; Dual appointment as ARUP Medical Director for the Toxicology and SAM labs and Faculty member and Professor in the University of Utah Department of Pathology.

<http://www.legacy.com/obituaries/saltlaketribune/obituary.aspx?n=francis-merrill-urry-fran&pid=175289178&fhid=29616#sthash.LEL7GIVj.dpuf>

American Academy of Forensic Sciences – Toxicology

Submitted by Dan Anderson, Section Secretary

The 2016 Annual meeting will be held February 22-27, 2016 in Las Vegas, NV and the theme of the meeting will be '*Transformation: Embracing Change.*' The Section Program Chair **Fiona Couper** (Fiona.Couper@wsp.wa.gov) and Co-chair **Nikolas Lemos** (nikolas.lemos@sfgov.org) are assembling an excellent scientific session that includes special sessions of DUID topics, the joint session of Toxicology and Pathology/Biology, and Pediatric Toxicology. Attendees will further enjoy the Annual Toxicology Lectureship along with the 4th annual Toxicology Luncheon and its festivities. Please plan on joining us - *Viva Las Vegas!*

**Society of Forensic Toxicologists,
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2015 S.O.F.T. COMMITTEE CHAIRS

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Committee Chair

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Membership.....	Bruce Goldberger, Ph.D., F-ABFT
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JAT Special Issue.....	Sumandeep Rana, Ph.D.
Awards.....	Erin Spargo, Ph.D., F-ABFT
Meeting Resource.....	Jennifer Limoges, M.S., DABC
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Vendor Liaison.....	Jarrad Wagner, Ph.D., F-ABFT

WEBMASTER

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TOXTALK® Deadlines for Contributions:

February 1 for March Issue

May 1 for June Issue

August 1 for September Issue

November 1 for December Issue

Future SOFT Meeting Destinations:

- 2015:** Atlanta, GA.....Oct. 18-23rd, 2015.....Robert Sears
- 2016:** Dallas, TX.....Oct. 16-21st, 2016.....Chris Heartsill/Erin Spargo
- 2017:** Boca Raton, FL.....Sept. 10-15th, 2017.....Ruth Winecker/Dan Anderson
- 2018:** Minneapolis, MN.....Oct. 7-12th, 2018.....Loralie Langman
- 2019:** San Antonio, TX.....Oct. 13-18th, 2019.....Veronica Hargrove/Brad Hall

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