ACMT/IST 2019 American-Israeli Medical Toxicology Conference Abstracts—Haifa, Israel

American College of Medical Toxicology¹

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Introduction

The American College of Medical Toxicology (ACMT) in conjunction with the Israeli Society of Toxicology (IST) is presenting the Third Joint American-Israeli Medical Toxicology Conference in Haifa, Israel, on November 19–20, 2019. ACMT and IST previously held joint conferences in 2010 and in 2013. This work would not be possible without the hard work and diligence of our conference organizers and abstract reviewers: Didi Bentur, Yaron Finklestein, Lewis Nelson and Paul Wax. Equally significant is the contribution of the ACMT staff (Adrienne Dunavin) and the Israel Poison Information Center staff (Vered Steiner) who helped manage the process. Congratulations to all the contributors whose work will be presented in Haifa.

Day 1

The Medical Challenge at the Chemical Terror Scene

Yuval Cohen
CBRN Branch, Israel Defense Forces, Israel

Since the 1995 Tokyo subway sarin attack, terrorist attacks involving weapons of mass destruction or other industrial chemicals present worldwide security and health concerns. On-scene medical triage and treatment in such events is crucial to save lives and minimize the deleterious effects of the

toxic agent involved. The challenges facing the emergency medical service (EMS) teams on scene include recognizing the event as a non-conventional attack involving a chemical agent, recognizing the nature of the agent and at last, treating the casualties accordingly. The wide range of potential chemicals that may be used in terror attacks and their diverse toxidromes render diagnosis extremely difficult. Taking in account that the medical treatment is usually supportive, the question that EMS personnel should be asking is not “what chemical was used” but “does the offending agent have an antidote.” This relevant question may change the treatment and prognosis of the patients.

Treatment of Acute Cyanide Poisoning: Time to Move Forward

Ophir Lavon
Carmel Medical Center, Haifa, Israel

Cyanide continues to pose a major threat for single and mass poisonings. Better and safer antidotes for cyanide poisoning are needed, especially for out-of-hospital treatment. After decades of lack of significant progress, the recent years are rich with studies evaluating novel compounds as counter measures for acute cyanide poisoning. Yet, there are still obstacles in the way to improve therapy and outcome and the road for an available and effective treatment is still long. Mechanisms of cyanide toxicity are more complex than previously recognized. While the inhibition of cellular respiration through cytochrome oxidase C and the development of metabolic acidosis are considered the main mechanism, more data from animal models indicate earlier central effect leading to mortality before acidosis is evident. Better understanding of the full acute insults of cyanide is cardinal to direct studies for new countermeasures, aimed to improve morbidity and mortality. New pathways for antidotal effect should be explored

Supervising Editor: Mark B. Mycyk, MD

✉ American College of Medical Toxicology
info@acmt.net

¹ American College of Medical Toxicology (ACMT), 10645 N. Tatum Blvd, Phoenix, AZ, USA

using of-the-shelf medications that may be effective in cyanide poisoning. Reliance on novel compounds is problematic as drug development, and approval is long and expensive. Research and development efforts should be focused on practical delivery devices of antidotes for the pre-hospital scenario. Combined protocols should be evaluated with more emphasis on supportive measures and diagnostic tools.

Preparation of General Hospitals in Israel to Mass Toxicological Event—from Doctrine to Drills

Eran Alon

Head of CBRN Sector, Hospital Preparedness Branch, Home Front Command, Israel Defense Forces

A mass-toxicological event (MTE) is a challenging emergency situation for a general hospital to deal with. Besides preparing the emergency department (ED) to handle a multi-casualty event, responding to a MTE requires a specific organization and preparedness. This includes training medical teams to wear personal protective equipment (PPE), preparing a controlled area for treatment and decontamination of exposed or contaminated casualties, and preparing a “clean” area for the treatment of decontaminated patients.

The doctrine of the Ministry of Health (MOH) for MTE requires hospitals to prepare a decontamination site outside the entrance of the ED in order to receive and decontaminate casualties within 20 min. Lessons from surprise MTE drills showed that most of the hospitals were able to prepare the designated decontamination site within 40 min or more. That led the Advisory Committee to the MOH for Toxicological Events to conduct a series of discussions during 2018 in order to better define how general hospitals should handle the first contaminated casualties arriving to the hospital, before the decontamination site is set up. As a result, the MOH doctrine of MTE for general hospitals was updated during 2019. The new doctrine defines a new form of a basic PPE that is easier to wear and function. Moreover, it has defined a first-level response for situations where casualties arrive before the decontamination site is ready for operation. In these cases, casualties will be urgently transferred to a controlled site inside the ED where life-saving treatment and bedside decontamination will be provided. The new doctrine is being implemented nowadays; it has been practiced in several drills during the last year, and the lessons will be reviewed by the Advisory Committee.

The Use of Social Media for Collecting Real Time Clinical Information: The Syrian Case

Yuval Cohen

CBRN Branch, Israel Defense Forces, Israel

Organophosphate (OP) nerve agents cause a classical clinical presentation of hypersecretion and miosis by inhibiting acetylcholine-esterase. If left untreated, symptoms may worsen and include seizures, respiratory failure, and death. Treatment includes atropine, an anticholinergic drug, oximes for reactivation of acetylcholinesterase, benzodiazepines as anticonvulsants, and respiratory support. In August 2013, sarin, a potent nerve agent, was dispersed in the eastern outskirts of Damascus. The attack killed 1400 civilians and caused severely injured thousands. The conflict in Syria is unique for being intensely covered in almost “real time” through social media networks. The photos and footage gave the world an inside look and allowed the recognition of the clinical syndrome well before the United Nations investigation confirmed the diagnosis of sarin poisoning. Using social media seems a novel approach to gather real-time clinical knowledge. This approach is probably most valuable in situations where there is no immediate and direct access to victims, such as war zones or natural disaster settings. As the use of social media grows and smartphones become more popular, each event generates more data. Systematic gathering of these materials could be used as part of clinical or epidemiologic investigations.

Eye Pathology, Respiratory Toxicity and Death Following Whole Body VX Vapor Exposure are Prevented Only by Repetitive Antidotal Treatment

Eugenia Block-Shilderman

Israel Institute for Biological Research, Israel

Exposure to the chemical warfare nerve agent VX causes severe cholinergic effects. If not appropriately treated, death ultimately ensues. A real-life scenario of VX exposure during a military conflict or a terrorist attack will most likely involve whole body exposure to VX vapor, including exposure via the respiratory route (inhalation exposure), dermal exposure, and exposure of the eyes. Based on our previously described whole-body vapor exposure system, we characterized in detail the clinical outcome, including respiratory dynamics, typical of whole-body exposure to lethal doses of VX vapor in freely moving rats. We show that a 15-min exposure to air VX concentrations of 2.34–2.42 mg/m³ induced a late (15–30 min) onset of obvious cholinergic signs, which exacerbated over time, albeit without convulsions. Marked eye pathology was observed, characterized by pupil constriction to pinpoint, excessive lacrimation with red tears (chromodacryorrhea) and corneal damage. Respiratory distress was also evident, characterized by a three–fourfold increase in Penh values, an estimate of lung resistance, and by lung and diaphragm histological damage. We further evaluated the efficacy of two different antidotal regimens—one comprising a single and the other repeated administration of antidotes—in countering the toxic

effects of the exposure. A single administration of TAB (the oxime TMB-4, atropine, and the anticholinergic and antiglutamatergic benactyzine) at the onset of clinical signs of poisoning afforded only limited protection (66% survival), with clinical deterioration including weight loss, chromodacryorrhea, corneal damage, increased airway resistance, and late death. In contrast, a combined therapy of TAB at the onset of clinical signs and repeated administration of atropine and toxogonin (ATOX) every 3–5 h, a maximum of five IM injections, led to 100% survival and a prompt recovery, accompanied by neither the above-described signs of eye pathology, nor by bronchoconstriction and respiratory distress. The necessity of recurrent treatments for successful elimination of VX vapor toxicity strongly supports continuous penetration of VX following termination of VX vapor exposure, most likely from a VX reservoir formed in the skin due to the exposure. These, combined with the above-described eye and respiratory pathology and absence of convulsions, are unique features of whole-body VX vapor exposure as compared to whole-body vapor exposure to other nerve agents and should accordingly be considered when devising optimal countermeasures and medical protocols for treatment of VX vapor exposure.

Fourth Generation Nerve Agents

Charles McKay
Hartford Hospital, CT, USA

The recent Novichok assassination attempt and “bystander” illnesses and death in the UK have raised some serious questions about clinical recognition of isolated occult non-volatile nerve agent exposures as well as many questions about education, information sharing, detection, workforce protection, and other response issues. While some of these questions are not yet clearly answered, certain principles and practical responses are clear.

What are the major concerns with exposure to the so-called fourth-generation nerve agents? What are the differences between countries in terms of education for first responders? This lecture will describe the US educational response that resulted in the National Security Council documents for a variety of stakeholder (available at the National Library of Medicine site: <https://chemm.nlm.nih.gov/nerveagents/FGA.htm>) and discuss some of the unresolved questions about safety and management when considering these agents.

Myths and Misinformation About Casual Dermal Exposure to Fentanyl Among First Responders

Lewis Nelson
Rutgers New Jersey Medical School, NJ, USA

There is escalating confusion and media hyperbole in the US about the risk of passive fentanyl exposure. This has led to misguided efforts to ensure the safety of emergency and law enforcement personnel through burdensome new regulations and policies and the implementation of expensive technology. Despite the rapid rise of illicit fentanyl beginning in 2013, the first report of passive casualties did not occur until a news account went viral in 2017. In this report, a police officer in East Liverpool, Ohio, USA, brushed a white powder off his uniform, lost consciousness within an hour, and responded to naloxone. This led the DEA to release recommendation, such as extensive personal protective equipment, that were impractical for job performance and potentially unsafe. There are no convincing reports of passive exposure leading to the development of a consistent toxicological syndrome nor having credible analytical toxicology testing. Descriptions of patients in these reports vary widely, including dizziness, blurry vision, pallor, weakness, and anxiety, occasionally with seizure-like activity and foaming at the mouth [<https://www.cdc.gov/niosh/hhe/pdf/2018-0113-3325.pdf>]. Response to naloxone appears to be non-pharmacologic in nature. Expectedly, advanced analytical testing of the drug samples often detects fentanyl(s). However, advanced analytical testing of biological specimens has been nearly uniformly negative. The high lipophilicity of fentanyl analogs hampers penetration of the stratum corneum. Even with permeation enhancers in transdermal fentanyl, hours are required to see elevations of serum fentanyl concentrations. Transmucosal absorption, while faster, is still relatively slow. Those who work in EDs and care for victims of fentanyl overdose are undoubtedly exposed to these drugs on patients’ clothing, skin, and paraphernalia. Traffickers, dealers, and people who use these drugs have direct contact with these substances at many stages in their distribution. Recent position statements issued by the American College of Medical Toxicology [www.acmt.net/Library/Positions/Fentanyl_PPE_Emergency_Responders_.pdf], NIOSH, and ONDCP [www.whitehouse.gov/ondcp/key-issues/fentanyl] assist medical directors, policymakers, and stakeholders involved in protecting and educating those with potential exposure. Because proving the complete absence of risk is not practical, the guidelines advance recommendations with an abundance of caution. For example, gloves should be worn when touching a product believed to contain fentanyl analogs. Entering a location with the possibility of airborne toxin should prompt the donning of particulate respiratory protection. Avoidance of eating or touching one’s mouth prior to handwashing and not entering environments that appear risky (e.g., multiple casualties) are attainable personal protective practices

Weaponized Opioids

Nicholas Connors

Medical University of South Carolina, SC, USA

The use of chemical weapons in areas of conflict has been a concern since antiquity. While the main focus of attention and preparation has been on agents such as nerve gases, sulfur mustards, and asphyxiants, opioids can be incapacitating and deadly when targeting people in a confined setting. Weaponized opioids have been used on a large scale at least once, most notably in 2002, by Russian special forces during the Dubrovka Theater hostage crisis in Moscow. During that incident, a chemical was administered through the theater ventilation system prior to the armed entry of special forces. Over 100 hostages were killed by the gas. While Russian authorities never officially identified the chemicals, residue collected from survivors isolated remifentanyl and carfentanyl. Before it became a scheduled substance in 2017, several companies in China exported carfentanyl cheaply for about \$2750 per kilogram. At 100 times, the potency of fentanyl the easy distribution of such a potent opioid has been a concern of the US Department of Defense. It has gained international attention as well and is banned from the battlefield under the Chemical Weapons Convention. Human symptoms are consistent with toxicity due to other opioids including depressed mental status, ventilatory depression, and death. In carfentanyl, exposures due to contaminated heroin large doses of naloxone were required for reversal. Public agencies appreciate the threat posed by weaponized opioids and industry contracts for the development of a nasal nalmefene, a long-acting opioid antagonist, have been awarded by the US Department of Health and Human Services under the Biomedical Advanced Research and Development Authority. Medications with opioid antagonism such as naloxone, naltrexone, nalmefene, and possibly buprenorphine can be considered when preparing for a response to this threat.

Dipyrone—a Good Medication with a Bad Reputation

Natalie Dinavitsner

Shamir Medical Center, Zerifin, Israel

Dipyrone, a weak NSAID, is used as analgesic and antipyretic medication in many countries worldwide. It is being marketed for almost 100 years. Its mechanism of action is probably by inhibition of a central COX-3, activation of the opioidergic system and cannabinoid system. More than 50% of the drug is protein-bound, with short half-life, and its elimination is mostly renal.

Dipyrone is registered in Israel from 3 months of age, and it is being sold as OTC. There are countries where it is a prescribed medication. Several studies have been performed with

dipyrone showing its efficacy and safety in fever reduction in children and adults, post-operative pain, migraine, and headaches. Rare adverse effects of dipyrone are anaphylaxis and agranulocytosis. Recently, the EMA issued a warning on dipyrone use during pregnancy and lactation, claiming that there is no information in these conditions. However, a consensus statement of several drug consultation centers in Israel, opposed EMA's decision, determining that the medication is compatible with pregnancy and lactation.

Data Sources Supporting Food and Drug Administration Drug Safety Communications

Daniel Shepshelovich

Shamir Medical Center, Israel

Introduction: Drug safety communications (DSCs) are the Food and Drug Administration's (FDA) primary tool for communicating important new post-marketing safety information to patients and healthcare professionals [1]. Our objective was to describe the sources of the initial safety signals that leads to DSCs and examine their associations with drug characteristics and subsequent label changes.

Methods: The study included all DSCs issued between January 29, 2010, when DSCs first became publicly available, and December 31, 2018, identified from the FDA's website [2]. We excluded DSCs for over-the-counter drugs. For each DSC, we determined the information source that served as the basis of the initial safety signal, categorized as data from the FDA's Adverse Event Reporting System (FAERS) [3], RCTs, and other sources. We used Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables to examine associations between information source and initial regulatory approval pathways, time between initial approval and DSC posting, characteristics of clinical studies included in the most recent drug label prior to DSC publication, and subsequent safety-related changes to drug label. We used Spearman's correlation testing to examine for changes in the number of DSCs issued annually. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary NC). Statistical significance was defined as a 2-sided $p < 0.05$.

Results: There were 228 DSCs issued by the FDA from 2010 through 2018. DSCs characteristic are shown in Table 1. The number of DSCs decreased with time ($\rho = -0.9$, $p = 0.005$). The most frequent information source that served as the basis of the initial safety signal were FAERS ($n = 87.38\%$) and RCTs ($n = 81.36\%$). Time from initial approval to DSC posting was significantly shorter for DSCs triggered by FAERS or RCTs versus other sources ($p < 0.001$) (Table 2). Common subsequent changes to drug labels included additional warnings and precautions and boxed warning.

Discussion: The leading initial sources of DSCs were the FAERS program and RCTs. Despite known under-reporting

of safety information to voluntary, passively collected pharmacovigilance programs, the large proportion of DSCs initiated by FAERS highlights FDA's reliance on the program for post-market drug safety monitoring. Similarly, the continued utility of RCTs for identifying new safety issues is at odds with recent legislation promoting the replacement of traditional RCTs with real-world data analyses to help support the approval of supplemental indications or the fulfillment of post-approval study requirements [4]. Our study shows that relatively few DSCs were initiated by real-world data.

Conclusion: FAERS and RCTs triggered most DSCs and were associated with shorter time from initial approval to FDA issuing DSCs. These data might inform clinicians and regulators of the current state of post-marketing toxicity monitoring and assist in guiding future improvement efforts.

Drug Induced Liver Injury: State of the Art

Javier Waksman
FibroGen, Inc., USA

Drug-induced liver injury (DILI), herbal-induced liver injury (HILI), and herbal and dietary supplement-induced liver injury are among the most difficult diagnoses faced by clinicians. Multiple drugs, herbs, and dietary supplements are associated with these conditions, the mechanism of injury can be diverse, and the diagnosis challenging due to the absence of specific biomarkers. Idiosyncratic (unpredictable) DILI constitutes the leading cause of attrition during drug development and one of the two most frequent causes for drug withdrawals, restrictions, and terminations. It can be severe and lead to acute liver failure and death. New emerging biomarkers, which could be useful in assessing DILI, include total keratin 18 and caspase-cleaved keratin 18, macrophage colony-stimulating factor receptor 1, high mobility group box 1, and microRNA-122. This presentation will discuss the current state of the art of DILI including diagnosis, risk factors, mechanisms, specific drugs (including biologics, and newly developed checkpoint inhibitors), and novel biomarkers of idiosyncratic DILI. In addition, the principles around detecting DILI in clinical trials will be discussed.

Novel Buprenorphine Formulations and Administration Methods for Opioid Agonist Therapy

Stephanie T. Weiss
Wake Forest Baptist Medical Center, NC, USA

The opioid epidemic continues to be a serious problem in Western countries including both the USA and Israel. According to the United States Centers for Disease Control and Prevention, in 2017, there were 70,237 drug overdose deaths in the USA alone, of which 67.8% (about

47,600) were due to opioid overdoses. Although sublingual opioid agonist therapy with buprenorphine, a partial mu opioid receptor agonist, has been shown to improve outcomes in patients with opioid use disorders, there are now several new long-acting buprenorphine formulations on the market that may be superior in terms of preventing diversion, misuse, or abuse of buprenorphine when compared with sublingual formulations. This presentation will discuss formulations of buprenorphine currently available on the market in the USA and Israel, and compare their advantages and disadvantages (including possible diversion, misuse, or abuse). Products to be discussed include sublingual or buccal buprenorphine/naloxone tablets and films, buprenorphine depot injections, and buprenorphine implants. Emphasis will be given to the specific pharmacological properties, prescribing considerations, and abuse potential of buprenorphine, including the transdermal buprenorphine patch as well as sublingual buprenorphine and long-acting buprenorphine formulations.

The Interaction between Direct Oral Anti Coagulants (DOACs) and Enzyme Inducing Antiepileptic Drugs: Potential Implications and Strategies

Mordechai Muszkat
Hadassah Medical Center, Mt. Scopus, Jerusalem, Israel

Direct oral anticoagulants (DOACs) have a more predictable dose-response relationship and fewer drug-drug interactions than vitamin K antagonists (VKA). Thus, DOACs are replacing VKA in the treatment of non-valvular atrial fibrillation and venous thromboembolism. However, the elimination of several DOACs is mediated extent via cytochrome P-450 (CYP450) enzymes (in part via CYP3A4/5) and P-glycoprotein (P-gp), potentially resulting in significant drug-drug interactions. DOAC interaction with CYP3A4/5 and/ or P-glycoprotein (P-gp) inhibitors may result in DOAC accumulation and increased bleeding risk, while interaction of DOACs with inducers of CYP3A4/5 and or P-glycoprotein (P-gp) may result in enhanced DOAC elimination and in sub-therapeutic concentrations, potentially leading to reduced efficacy and thrombotic and/or ischemic events. Several common antiepileptic drugs (AED), such as carbamazepine, phenobarbitone, phenytoin, as well as other agents, are known to be inducers of protein expression, including CYP450 enzymes and P-gp. Thus, co-administration of these medications together with DOACs can reduce the efficacy of DOACs treatment. However, there is uncertainty regarding the clinical impact of this interaction. The aim of our work is to review the impact of co-administration of DOACs and enzyme inducing antiepileptic medications on the efficacy of treatment with DOACs and on DOAC concentrations.

Herbal-Induced Liver Injury: Clinical and Immunogenetic Causality Assessment

Manuela Neuman
University of Toronto, Canada

Background: Severe cutaneous adverse reactions (SCARs) culminate with Steven-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) (mortality 20–60%). Drug-induced and herbal-induced liver injury (DILI/HILI) may result in removal from the market of a useful drug by regulatory agencies. The injury to the liver may occur as an unexpected reaction to a therapeutic dose of a drug (idiosyncratic reaction), or as an expected therapeutic effect of the direct toxicity of a drug taken in a large enough dose to cause liver injury. We present both clinical and laboratory evidence implicating mitochondrial toxicity and an immune response leading to a hypersensitivity reaction.

Objectives: (1) Correlate the severity of SJS/TEN or DILI/HILI with *in vitro* lymphocyte toxicity assay (LTA) in order to determine the incriminated drug of SJS/TEN, DILI/HILI; (2) identify defects in immuno-responses; (3) confirm the biomarker validity of clinical outcomes by using *in vitro* drug-induced inflammatory cytokine cascade and mitochondrial succinate dehydrogenase activity; and (4) conduct a pharmacogenetic analysis of HLA 1502 subtypes in Han-Chinese patients with epilepsy.

Methods: We studied 90 patients that presented SJS/TEN (10 to Ibuprofen, 65 (40 Han Chinese) to anti-epileptics, 20 to allopurinol). The DILI/HILI patients were treated with denosumab, Saxeda, methotrexate, a combination of tea and protein. The succinate dehydrogenase activity was the measure of cell viability. LTA toxicity higher than 15% was considered positive. Interferon (IFN) was measured in sera. IFN-gamma test calculates the IFN-gamma excreted in media by cells not exposed to drug(s)(pg/mL) versus cells exposed to drug(s) (pg/mL).

Results: (1) A perfect correlation was observed between the LTA positive $r = 0.90$ and the clinical diagnosis in SJS/TEN and DILI/HILI. (2) IFN-gamma showed a high level of immune activation (140–1220 pg/mL) when compared to control in sera (30–90 pg/mL).

Conclusions: Prediction of an IHSR using *in vitro* LTA and IFN-gamma techniques ensures safe administration of therapies.

Day 2

Arum palaestinum Poisoning—Revenge of the Witch

Aus Maree
Hadassah Medical Center, Mt. Scopus, Jerusalem, Israel

Background: Arum palaestinum, also known as “Mekhalet El-Ghoule,” which literally means “the paintbrush

of the witch” is one of 26 species of the Arum genus of the Araceae family. Different species of the plant are distributed through the Mediterranean Region, Western Asia, and Europe. The leaves and seeds of the plant contain needle-shaped oxalates crystals that upon exposure cause irritation to the affected tissue (oral cavity or GI tract). Surprisingly there is no available literature supporting the epidemiology and clinical manifestations of poisoning by this plant.

Methods: All pediatric Arum palaestinum exposures reported to The Israel National Poison Information Center during 2017 were reviewed retrospectively from the IPIC computerized data system. Demographic data and clinical data were extracted from those digital files.

Results: Fifty-three patients files were reviewed with slight male predominance (58% vs. 42%), and median age of exposure was 2.5 years (9 month to 15 years). Exposure occurred at home in most cases (47%) followed by outdoor exposure in 40% of the cases. In 66% of the cases, minor clinical manifestations were reported, mainly erythema and mouth irritation, agitation, and drooling. Thirty-four percent of the cases were asymptomatic. In 17% of the cases, the IPIC recommend referral to an ambulatory facility, and other 15% of the cases were referred to the emergency department. There were no cases of severe poisoning, upper airways compromise, or death.

Discussion: Arum palaestinum poisoning is one of the most common pediatric plant poisoning in Israel. Our study supports with clinical data for the first time the common knowledge that this poisoning is self-limited, confined to the affected mucosa, and most likely does not necessitate any intervention.

Environmental Exposures of Firefighters in Israel

Elkana Kohn
Shamir Medical Center, Israel

Background: Firefighters are occupationally exposed to various contaminants and toxic gas fumes emitted to the environment during combustion. Electronic equipment, plastics, textiles, furniture, mattresses, cars, fuels, paints and many other consumer products contain heavy metals, Polybrominated diethyl ethers flame retardants (PBDEs) and many other chemicals. “These compounds are released into the environment and then leach into the human body. There is a growing concern about their negative impact on population's health. Although the general population is exposed to these contaminants, there are sub-groups with occupational risk of high exposures. Some of these groups include firefighters, electronic recycling workers, and furniture factories workers. In this study, we will analyze BFRs, phthalates and BTEX levels in firefighters' blood and urine and compare them to levels of these contaminants in a control group of men from other occupations.

Objectives: To evaluate PBDEs, heavy metals and BTEX levels in blood and urine of fire fighters and control group; and to evaluate the association between levels of these substances and general health status.

Methods: BFRs levels were measured in serum and heavy metals in urine. Health condition of the participants was evaluated by lifestyle questionnaires physical examination and blood lab tests. Participants answered questionnaires and gave blood and urine samples. A physician interviewed and examined each participant.

Results: One hundred and ten firefighters from four fire stations were recruited. Mean urine metal concentrations were (in mcg/L): Cr 0.48, Ni 0.73, As 17.29, Cd 0.38, Hg 0.63, Pb 0.41, Se 53.53, Tl 0.23. Mean serum PBDEs were (in ng/L, (> LOQ)): BDE-47: 46.85 (40), BDE-66 : 33.53 (14), BDE-100: 31.73 (6), BDE-99: 32.93 (21), BDE-85: 22.63 (2), BDE-154: 27.05 (23), BDE-153: 35.4 (32), BDE-183: 42.63 (1). BDE-28 was undetectable in all samples.

Conclusions: Firefighters blood and urine levels of heavy metals and PBDEs are relatively low, compared to other populations in the world. We will further investigate firefighters' exposures with the data and samples collected in this study.

Environmental Tobacco Smoke Exposure Among Children With and Without Respiratory Symptoms: A Case-Control Study

Ayal Grinshpun
Shamir Medical Center, Israel

Background: Environmental tobacco smoke (ETS) refers to the smoke that involuntarily inhaled by those who are not necessarily smokers but are in close proximity to others who smoke. Multiple studies worldwide have found that exposure to ETS is linked to many health problems including asthma and is associated with its severity.

Objective: Estimation of baseline ETS exposure among children with and without respiratory symptoms in a pediatric emergency department (ED)

Methods: We performed a case-control study during 2014 at the Asaf Harofeh Medical Center. Patients were enrolled, urine samples were collected from the children, a questionnaire was completed by the accompanying parent and relevant medical, socio-demographic information was extracted from the child's medical records.

Results: A total of 150 children were enrolled: 50 cases (with respiratory symptoms) and 100 controls (with gastrointestinal symptoms). Parental tobacco smoke was similar (42–43%) in both groups and the father was the primary smoker. Exposure to ETS in “public areas of the building,” and in playgrounds was more common among children with respiratory symptoms (38.6% vs 18.5% , $p = 0.01$ and 37.8% vs 20.2% $p = 0.02$, respectively).

Children from families in which the father had less than 12 years of schooling had odd ratio (OR) of 8.2 to be exposed to ETS than children from families whose father had more than 12 years of schooling ($p < 0.001$).

Parents' viewpoints were tested on their agreement on whether public places should be non-smoking zones. There were no significant differences between parents of cases and parents of controls; most of the parents agreed that the suggested places in the questionnaire should be clean from smoke (84–97% depending on the area).

Conclusions: Children with and without respiratory symptoms are highly exposed to ETS. There was a high percentage of parents who smoke among children with known exposure to ETS. For further assessment of children exposed to ETS there is a need for additional monitoring of exposure to ETS while planning health programs to minimize this exposure. We also recommend training smoking parents (especially fathers) and parents of children with respiratory symptoms to avoid exposure to ETS and make this an important issue for discussion in the general population and in the media in order to help promote laws and enforcement.

Impact of a Toxicology Consultation Service in a Large Tertiary Care Teaching Hospital

Miguel Glatstein
Sourasky Medical Center, Israel

Medical Toxicology has been recognized as a subspecialty by the American Board of Medical Specialties (ABMS) since 1992. Over the past twenty-five years, medical toxicology has emerged as an important fellowship program, with many medical toxicologists completing a prior residency program in emergency medicine. Currently in Israel this subspecialty is not widely available via bedside consultation, therefore when consultation regarding suspected poisoning or exposure is required it is directed to a poison center by phone. In collaboration with our tertiary care center, an Israeli-certified pediatric emergency physician was sent to complete an International fellowship program at the Rocky Mountain Poison Center in Denver, Colorado. The aim of this study was to describe the implementation of a bedside toxicology service including the structure and organization of the service, the spectrum of clinical cases received, the barriers to implementation, as well as the benefits and future goals of the service. There were 293 consultations, 76% of those occurring bedside. The service included pediatric and adult patients. The transition to a consult service required a culture change. After promotion of the service and full attending coverage, requests for consultation increased. In collaboration with toxicologists from different institutions, a consultation service was established. Bedside medical toxicology consultation was an important change at the institution.

A Bloody Mess: Brodifacoum and K2

Michael Mullins

Washington University School of Medicine, St. Louis, MO, USA

Synthetic Cannabinoid Receptor Antagonists (SCRAs)—commonly called “K2” or “Spice”—have appeared in North America and Europe for several years. Several K2 outbreaks have occurred in cities in the US. In March 2018, a peculiar K2 outbreak occurred in Illinois with unusual bleeding and extremely high INR values. Analysis soon revealed the consistent presence of brodifacoum, a “superwarfarin” rodenticide. Brodifacoum has extremely high affinity for the vitamin K epoxide reductase 1 (VKOR) enzyme and high lipophilicity. These characteristics cause brodifacoum to persist in the body for very long intervals. The Illinois Poison Centre and the Illinois Department of Public Health rapidly coordinated the response to the outbreak, provided timely and accurate advice to physicians, and secured a stockpile of oral vitamin K (phytonadione), which is quite expensive in the US. Patients often received 4-factor prothrombin complex concentration or fresh frozen plasma for control of severe bleeding. Patients often exhausted Vitamin K supplies in local hospitals. After initial control of bleeding and improvement in INR, patients required high doses of vitamin K for at least a month in most cases. The outbreak spread to neighboring states. Brodifacoum appeared with several related SCRAs in different locations with over 300 cases and at least 10 known deaths. The outbreak peaked in late spring but persisted into early autumn. Incidence of new cases rapidly declined after law enforcement arrested key drug dealers and seized kilogram quantities of brodifacoum-laced K2. The apparent aim of adding brodifacoum to K2 was to amplify or prolong the psychoactive effect by inhibiting drug metabolism. Vitamin K is the primary treatment, but it remains expensive in the USA. Potential adjunct treatments may include oral cholestyramine (cholesterol binding resin) or possibly intravenous lipid emulsion. It is likely that a similar outbreak will occur and will challenge healthcare resources again.

Trends of Intentional Drug Overdose Among Youth: A Population-based Cohort Study

Yaron Finkelstein

Hospital for Sick Children, Toronto, ON, Canada

Background: Intentional overdose is the most common form of self-harm in adolescents globally. We explored temporal trends in intentional overdose among youth.

Methods: Using multiple linked healthcare databases, we conducted a population-based cohort study in Ontario, Canada, from 2002 to 2015. We included all patients aged 8

to 20 years who presented to an emergency department (ED) or were hospitalized for intentional overdose, stratifying by age and agent(s) consumed. We determined the annual incidence of intentional overdose over time. For context, we contrasted these data against the annual incidence of select unintentional injuries (laceration of face or scalp, upper extremity fracture, and accidental burn) in the same group over the same period.

Results: We identified 31,419 unique intentional overdose events in youth, with a striking U-shaped trend apparent over the study period. From 2002 to 2010, hospital presentations for intentional overdose gradually declined. However, from 2010 to 2015, ED visits increased by 75% and hospital admissions doubled. The sharpest increases were observed in adolescents aged 14 to 17 years, and the most commonly implicated substances were acetaminophen, antidepressants and NSAIDs. Over the study period, intentional overdoses involving antidepressants nearly doubled and those involving acetaminophen increased by 50%. In contrast, we observed steady and sustained declines in rates of hospital care for accidental injuries in the same population over the same period.

Conclusions: Since 2010, intentional overdoses have increased among youth, while other forms of unintentional injury have continued to decline. Further research is needed to understand the reasons for the unexpected rise in intentional overdose in adolescents, and strategies should be developed to mitigate this phenomenon.

The Increasing Rate of Suicide Attempts by Self-Poisoning in the US Among Youth and Adolescents with a Focus on Diphenhydramine—Another Emerging Public Health Concern

Erica Liebelt

University of Washington School of Medicine, Seattle, WA, USA

Suicide rates in the USA have been steadily increasing in recent decades, especially in the female adolescent age group. Diphenhydramine (DPH) is a widely available over-the-counter (OTC) drug with a history of being misused and/or abused, and is now being ingested for self-harm/suicide. The purpose of this presentation is to discuss general sex- and age-specific increases in suicide attempts by self-poisoning in the USA among youth and adolescents with a specific focus on the increasing rate of intentional diphenhydramine exposures. Published literature reporting on the incidence and outcomes from intentional suspected-suicide self-poisoning (SSSP) in youth and young adults ages 10–24 years old will be reviewed. Specifically, in youth 10–15 years old, there has been a significant increase in the number and rate of SSSP from 2011–2018, from 125 to 299%. In addition, the percentage of cases with a serious outcome, major effect or death

increased over time. A retrospective observational study looked at trends in intentional DPH self-poisoning in individuals ages 10 and older using the National Poison Data System (NPDS) database over an 11-year period, from 2005 to 2016. Selected results to be discussed include 158,774 total intentional DPH exposures reported with females accounting for 63.1%. Intentional DPH exposures increased from 3.97 per 100,000 to 6.17 per 100,000 (55% relative change.) Increasing trends were most marked in the 10–14-year-old group which showed a 218% increase. The increase in the 10–14-year age range was predominantly due to suicide attempts (263% increase). The percent of DPH exposures classified as moderate or severe increased by 38.8% and 33.9%, respectively. Major adverse clinical effects increased 9.9% across all age groups. Specific increases were seen in the incidence of metabolic acidosis, rhabdomyolysis, and dysrhythmias/ECG changes. Death was rare but showed a small increase (3.6%) across all age groups.

Abuse of Nonscheduled Medications and Nonprescription Drugs

Wendy Klein-Schwartz

University of Maryland School of Pharmacy, MD, USA

While prescription opioid abuse is well described, there are less data and awareness of abuse of other “licit” medications. Abuse of nonscheduled medications and nonprescription drugs has been reported. Reasons for abuse of these medications include desired pharmacologic effects, belief that use of these drugs is more socially acceptable and safer compared to illicit drugs and relatively easy access. Sometimes these drugs are used to enhance the effects of illicit drugs or for self-treatment of opioid withdrawal. Examples of abused prescription drugs are psychoactive medications (e.g., bupropion, gabapentin, quetiapine, trazodone, venlafaxine), skeletal muscle relaxants (cyclobenzaprine, baclofen), promethazine, and clonidine. Nonprescription drugs include dextromethorphan and loperamide. This presentation will describe abuse and misuse with a focus on information obtained from poison center data. Epidemiology including trends over time, demographics, routes, clinical effects, and management sites will be addressed. Studies on abuse of bupropion, quetiapine, venlafaxine, and promethazine using National Poison Data System (NPDS) were conducted by this poison center. Trends varied with decreasing prevalence of abuse of venlafaxine (2000 to 2016) and increasing prevalence of abuse of bupropion (2000–2013) and promethazine (2002–2012). The majority were males for bupropion, quetiapine, and promethazine combination formulations, while gender distribution was close to even for venlafaxine and promethazine alone. The majority of abuse cases occurred in adolescents followed by young adults in their 20s, and the

route was primarily ingestion for all four drugs. For promethazine, quetiapine, and venlafaxine, the majority of patients were treated/released from emergency department (ED) with approximately 15–23% admitted for medical care. For bupropion, almost half the patients were admitted (~47%) and close to 37% were treated/released from ED. Prescribers and pharmacists should be aware of the potential for abuse of these medications.

Cannabis Among Adolescents—The Emerging New Reality

Gideon Koren

Shamir Medical Center, Zerifin, Israel

In November 2012, voters in Washington State legalized nonmedical (retail) cannabis for people > 21 years (Initiative 502), and the markets opened in July 2014. There are serious concerns among parents and pediatricians about the impact of these changes on large numbers of adolescents. That has led to increasing numbers of important studies to guide policy and prevention. In a study of 84 adolescents-young adults who regularly used cannabis, they were randomly assigned to continuation or d/c cannabis (with TDM). Discontinuation was associated with improved verbal memory but no effect on attention. Blevins et al have shown in 2018 no significant differences pre- and post-policy in rate of use by adolescents and no significant increases in norms, attitudes, or perception of risk. Similarly, there was no evidence of post-policy increase in heavy-using adolescents’ rates. In contrast, there is epidemiological evidence of increased cannabis potency, increased risk of psychosis, decreased spatial working memory, and recall increased reports of severity of cannabis dependence. In Montreal, a study measured THC initiation at grades 7, 9, and 11. At grade 6, students were 1.8–2.8 more likely to initiate if their parents were using in the past year. In The 2015 Youth Risk Behavior Surveillance Survey, the prevalence of early sexual intercourse was 15.3% Among THC users before age 15 the OR was 4.2–6.7; OR 9 among boys, 2.8 among girls. Among 527 adolescents in routine care, 146 affirmed first year use of THC, which was associated with increased risk of anxiety, paranoia, hallucinations, and depression. There were more symptoms among frequent users, those meeting criteria for cannabis use disorder. Another study showed strong association between adolescent THC and poor adults outcome. Among 47 adolescents reporting using Cannabis only once or twice, there was increase in grey matter volume. The authors summarized that

“We don’t really know for sure why. We also don’t know if it’s because of the cannabis, or they could have preceded the cannabis” (Garavan). In a systematic review of 37 studies including 23,317 individuals, there was increased risk for developing depression among cannabis

users, more suicidal ideation and attempts, but no increased risk for anxiety. The Chicken and Egg effect? Is it possible that kids starting cannabis earlier are more prone to psychiatric morbidity because of the very fact that they experiment early (i.e., it is part of their personality?) This is supported by Tonkins (2002) study. It is likely that the premorbid personality of adolescent cannabis users render them much more likely to exhibit and suffer from psychiatric disorders. Use of cannabis is a marker of premorbid psychiatric morbidity.

Fatalities in Poisoned Patients Managed by Medical Toxicologists

Nir Friedman

The Toxicology Investigators Consortium; Safra Children's Hospital - Sheba Medical Center, Israel

Background: Poisoning is a leading cause of injury-related death in the USA. Toxicology Investigators Consortium (ToxIC) Case Registry, established by the American College of Medical Toxicology, prospectively captures patients who were directly cared for and managed at the bedside by medical toxicology services. We sought to describe exposure cases who presented to Emergency Departments (ED) across ToxIC sites, which despite direct bedside care by medical toxicologists resulted in patient fatality.

Methods: We identified all cases in the ToxIC Case Registry that resulted in fatality after hospital presentation over the 6-year study period. We collected data on patient demographics and clinical information including age group, sex, circumstances for exposure, route of exposure, substances involved, presenting signs and symptoms, and management prior to death.

Results: Of 46,232 recorded cases in the registry over the study period, 268 (0.6%) fatalities met the inclusion criteria and comprise the study cohort. There was no sex predominance (138 females; 51.5%) and 27 (10.1%) were pediatric fatalities. In 195 (72.7%) patients, exposure was intentional. In 175 (65.3%) patients, fatality was associated with exposure to pharmaceuticals. The leading substances resulting in death were non-opioid analgesics, followed by opioids (72% prescription opioids), cardiovascular, sedatives, antipsychotics, antidepressants, and sympathomimetics.

Conclusions: Most ToxIC registry exposures resulting in death involve intentional exposures, with non-opioid and opioid analgesics being the most commonly lethal agents, and without sex predominance. One in 10 fatalities involved a child.

Quality Performance Measures in Medical Toxicology

Paul Wax

University of Texas Southwestern, Dallas, TX, USA

Background: The Centers for Medicare and Medicaid Services (CMS) has overseen the development of hundreds of quality measures by national medical societies directed at areas with perceived practice performance gaps. Given the absence of quality measures in medical toxicology (MT), beginning in 2016 the American College of Medical Toxicology (ACMT) developed a program specific for MT patients.

Methods: In 2016, ACMT convened a task force to develop quality measures for medical toxicology. In December 2017, Centers for Medicare and Medicaid Services (CMS) approved six quality measures that could be used to evaluate the care of a MT patient on the following topics: opioid misuse screening, pregnancy testing, timely ECG assessment in drug ingestions, appropriate treatment of acetaminophen ingestions, assessment of suspected toxic alcohol exposures, and repeat assessment of salicylate concentrations in overdose patients. Beginning January 1, 2018, data on these performance measures was collected as part of the CMS-approved ToxIC Qualified Clinical Data Registry (QCDR), a new component of the ACMT ToxIC Registry.

Results: In 2018, 14 medical toxicology sites that cared for patients at the bedside participated in the ToxIC QCDR. Depending on the metric, data was collected on 21 to 1273 cases during this first year. Performance rates varied from a low of 21.2% for the acetaminophen measure to a high of 76.4% for the pregnancy measure.

Conclusion: Medical Toxicologists are now able to report on quality measures to evaluate the treatment of MT patients. Initial data collection will allow for valuable benchmarking of current practice. Valuable lessons were learned from this first year of data collection.

Poison Center Consultations and Legal Liability

Ophir Lavon

Carmel Medical Center, Haifa, Israel

The medical profession is continuously challenged by legal obligations. While the aim of the law and regulations is to ensure adequate treatment, it imposes much burden and difficulties. The medical staff may be faced with legal allegations. Poison centers are unique institutions with various configurations, affiliations, and operational systems. Their staff holds several professional disciplines, with physicians usually in the minority. Awareness and knowledge of all staff members in poison centers to all aspects of legal liability of their work need to be addressed and validated. Proper documentation is pivotal, and appropriate methods of recording should be guaranteed. Patient confidentiality should be kept at the highest level. Access to medical data should be restricted and managed appropriately. Use of informal methods of communication (personal mail, WhatsApp, etc.) for correspondence, including text, images, and videos is problematic and should be regulated.

Patient consent, at least orally, for the exchange of data in various forms should be received and recorded. Surveillance of the quality and appropriateness of the consultations should be carried out repeatedly. Errors or near misses should be investigated in order to learn and improve. It is advised to present the lessons learned from these events to all the staff members. In addition, poison centers should verify that their insurance is adequate for their activities.

Lack of Predictive Value of Provoked Urine Test Results in the Determination of Toxic Exposures

Jeffrey Brent

University of Colorado, School of Medicine, CO, USA

Provoked urine testing (PUT) involves the determination of urine metal concentrations following chelator administration. Because it is likely that such testing may cause urinary excretion of metals to increase beyond reference ranges, even in the absence of significant exposures, such testing is considered to be an invalid predictor of metal toxicity. Nevertheless, PUT is widely utilized by some practitioners, and patients with results indicating urinary metal concentrations exceeding reference ranges may present to clinical practices for evaluation for possible metal toxicity. Interpretation of such testing results is hampered by a lack of data assessing the predictive value of PUT results for the diagnosis of metal toxicity. This presentation summarizes the results of a prospective assessment of the utility of PUT in predicting the likelihood of metal toxicity as assessed by medical toxicologists. The Toxicology Investigators Consortium (ToxIC), a prospective study of all cases treated at the bedside or in a clinic by medical toxicologists, collects data on patients presenting to medical toxicology clinics with PUT since 2012. After toxicologic evaluation, medical toxicologists assessed whether each patient's presentation represented a true toxic exposure. Between 2012 and 2017, 106 patients presented with PUT data to medical toxicology clinics participating in ToxIC. Thirty-two patients were excluded because a formal determination of whether they had a toxic syndrome was not made. Of the remaining 74 patients, 16 were determined to have signs or symptoms related to a toxic exposure. However, for 13 of these patients, the exposure was to a substance not implicated by their PUT. Only three patients were determined to have metal-related toxicity. All three had syndromes related to mercury exposure. The positive predicted value of PUT for the determination of metal toxicity was 4%. Based on these data, PUT is a highly unreliable predictor of toxic metal exposures.

Toxicity Assessment of Disposable Medical Devices

David Stepensky

Ben-Gurion University of the Negev, Israel

Disposable medical devices (DMDs) release potentially toxic leachable materials during their use. *In vitro* safety assessment of DMDs is usually performed using L-929 mouse keratinocytes. However, these cells do not represent the cells that are exposed to the DMDs' leachables in the body. For instance, cells that line the patient's blood vessels (i.e., vascular endothelium cells) and circulating cells are predominantly exposed to the leachables from the infusion sets. On the other hand, cells that line the urinary tract (i.e., urinary epithelium cells) are predominantly exposed to the leachables from the Foley catheters. During the several recent years, we developed new *in vitro* methods for safety assessment of DMDs based on the cultures of cells that are exposed to the specific DMDs *in vivo*. We applied these methods for extensive toxicity assessment of leachables from different DMDs. We investigated items from a variety of manufacturers that varied in design and storage time. Furthermore, we performed detailed assessment of the mechanisms and kinetics of cell death induced by the leachates from different types of DMDs, and identified the most robust tests for *in vitro* DMD toxicity assessment. In our presentation and accompanying posters, we will present the major outcomes of our research, and their implications for the DMDs quality control and assurance at the specific stages (manufacture, choice, storage, and use) that govern their clinical safety.

Hyperbaric Oxygen (HBO) Therapy for Toxicologists: Under Pressure

Peter Akpunonu

University of Kentucky, KY, USA

This presentation is a brief review of Undersea & Hyperbaric Medicine (UHM) with a discussion of things to come. The presentation will start with a brief review UHM history, followed by dive physics. There will be a review of the efficacy and research regarding hyperbarics for methemoglobin, cyanide, and longer discussion of carbon monoxide toxicity, followed by a discussion of current research in hyperbarics and what that means for the future.

A Quick Trip Through the QT Nomogram

Michael Mullins

Washington University School of Medicine, St. Louis, MO, USA

The QT nomogram is superior to most formulae that attempt to "correct" QT for heart rate. Compared to the Bazett, Fredricia, and other QT corrections, the QT nomogram provides similar sensitivity for arrhythmia events while having superior specificity. The use of the QT may decrease

unnecessary resources and monitoring for patients at low risk of arrhythmia. The nomogram line is a graph of a polynomial equation. Clinicians may have difficulty in applying the nomogram without a graphic depiction. A simple linear calculation allows easy estimation of the value of the QT nomogram (X) for any heart rate (HR) above 65 bpm. We used data from Isbister et al. originally describing the QT nomogram; the QT nomogram and the Linear Approximation appear on the same graph (Fig. 1). The Linear Approximation is $X = 484$ ms when $HR \leq 65$ bpm and $X = 484 - 2.5 \text{ ms} \cdot (HR - 65)$ when $HR > 65$ bpm. For every heart rate between 30 and 155 bpm, we calculated the difference (expressed in percent of the QT nomogram value) between the derived and approximated lines. The QT nomogram is linear for rates below 65 bpm and nearly linear at rates above the inflection point near 65 bpm. The Linear Approximation has maximum deviations of $+ 0.6\%$ to $- 7.5\%$. All deviations with an absolute value $> 1\%$ occur at heart rates > 130 . The linear approximation closely fits the derived QT nomogram line. A simple arithmetic calculation can quickly discern whether a QT-HR pair is above or below the nomogram line without reference to the graph or an online calculator. The linear calculation estimates within 1% of the QT nomogram for all heart rates up to 130 bpm.

Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case-control Study

Yaron Finkelstein

Hospital for Sick Children, Toronto, ON, Canada

Objective: To examine the association between montelukast prescription and neuropsychiatric events in children with asthma.

Methods: A matched, nested case-control design was used to identify cases and controls from a cohort of children aged 5 to 18 years with physician-diagnosed asthma from 2004 to 2015, in Ontario, Canada, prescribed an asthma maintenance medication. Cases were children with a hospitalization or emergency department visit for a neuropsychiatric event. Cases were matched to up to four controls on birth year, year of asthma diagnosis, and sex. The exposures were dispensed prescriptions for montelukast (yes/no) and number of dispensed montelukast prescriptions in the year prior to the index date. Conditional logistic regression was used to measure the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for montelukast prescription and neuropsychiatric events. Covariates in the adjusted model included sociodemographic factors and measures of asthma severity.

Results: Eight hundred ninety-eight cases with a neuropsychiatric event and 3497 matched controls were included. Children who experienced a new-onset neuropsychiatric event had nearly two times the odds of having been prescribed montelukast, compared to controls (OR 1.91, 95% CI 1.15–

3.18; $p = 0.01$). Most cases presented for anxiety (48.6%) and/or sleep disturbance (26.1%).

Conclusions: Children with asthma who experienced a new-onset neuropsychiatric event had nearly twice the odds of having been prescribed montelukast in the year prior to their event.

Clinicians should be aware of the association between montelukast and neuropsychiatric events in children with asthma, to inform prescribing practices and clinical follow-up.

Conducting Multicenter Medical Toxicology Research Network through the Toxicology Investigators Consortium

Paul Wax

University of Texas Southwestern, Dallas, TX, USA

Objective: In the past, few medical toxicologists in the USA provided direct care for patients at the bedside. Consequently, the most common poisoning research methodology employed poison center data collection. With the growth of the medical toxicology specialty, an increasing number of medical toxicologists now provide direct care for patients at the bedside. In 2010, the American College of Medical Toxicology established the Toxic Investigators Consortium (ToxIC) to provide a national network platform for multicenter collaborative research. We investigated the research output of ToxIC from inception in 2010 to the August 2019.

Methods: Research output were measured by several different variables including the number of investigators, research sites, hospitals, case accrual, abstracts presented, published papers, and extramural funding obtained. Data was obtained from the ToxIC Annual Reports and internal grant and publications tracking records.

Results: A total of 68,000 cases were reported to the ToxIC Registry from January 2010 to August 2019. These cases were entered from 45 sites who provide bedside care at 69 hospitals. More than 100 medical toxicologists participated in the data collection. Aside from the core registry data collection, seven sub-registries were set up during this period to collect more detailed data on a variety of toxicological research topics. During this 9.5-year period, 120 abstracts were presented at national and international meetings and 38 manuscripts were published in the peer review literature. Grant funding was obtained from the NIH, FDA, and industry. Total grant funding to date has exceeded \$1,500,000, about $\frac{1}{2}$ from governmental sources and $\frac{1}{2}$ from industry.

Conclusion: Constructing a large multicenter medical toxicology research network resulted in more than 100 abstracts and 30 papers published in its first 8 years. Maintaining such a network requires ongoing and continuous grant support.

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