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ORIGINAL ARTICLE

The Toxicology Investigators Consortium Case Registry-the 2018 Annual Report

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Abstract

The Toxicology Investigators Consortium (ToxIC) Registry was established by the American College of Medical Toxicology (ACMT) in 2010. The Registry collects data from participating sites with the agreement that all bedside medical toxicology consultation will be entered. The objective of this ninth annual report is to summarize the Registry's 2018 data and activity with its additional 7043 cases. Cases were identified for inclusion in this report by a query of the ToxIC database for any case entered from 1 January to 31 December 2018. Detailed data was collected from these cases and aggregated to provide information which included demographics, reason for medical toxicology evaluation, agent and agent class, clinical signs and symptoms, treatments and antidotes administered, mortality, and whether life support was withdrawn. A total of 51.5% of cases were female, 48% were male, and 0.6% transgender. Non-opioid analgesics were the most commonly reported agent class, followed by antidepressants and opioids. Acetaminophen was once again the most common agent reported. There were 106 fatalities, comprising 1.5% of all registry cases. Major trends in demographics and exposure characteristics remained similar to past years' reports. Sub-analyses were conducted to describe exposures in elderly patients, addiction consultation practices, and risk factors for bupropion-induced seizures. The launch of the ToxIC Qualified Clinical Data Registry (TQCDR) is also described.

Keywords Poisoning · Overdose · Surveillance · Epidemiology · Medical Toxicology

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Introduction

The year 2018, the ninth full year of operation of the Toxicology Investigators Consortium (ToxIC), was again marked by a number of notable achievements and continued robust data collection. This report summarizes the major aspect of data collected over the year. Major changes and achievements are described in this section of the Report.

In 2018, ToxIC had 40 active sites composed of 73 facilities. A total of 7043 new cases were enrolled. This brings the total number of cases in the ToxIC database accumulated since the Consortium started in 2010, to 66248 by December 31, 2018.

There were 17 new studies proposed by ToxIC investigators in 2018, of which 13 were approved. These new studies were:

(1) Risk Factors for Serotonin Syndrome Secondary to Bupropion Overdoses as Reported in the ToxIC Registry
(2) Co-exposure to Ethanol and Drugs of Abuse Among Adolescents (10-18): Variation in Clinical Characteristics among Events Presenting to Hospital by Race/Hispanic Ethnicity
(3) Kratom (Mitragyna speciosa) Use Resulting in Hospitalization-Common Reported Co-Ingestion and Clinical Characteristics
(4) Association of Seizures in Tramadol Overdoses Treated with Naloxone: A Report from the ToxIC Registry
(5) Inpatient methadone poisoning trends in the US
(6) Marine Envenomations Reported to ToxIC
(7) Use of octreotide by medical toxicologists in poisoned patients with all-cause hypoglycemia
(8) Protective Effects of Benzodiazepines in Overdose
(9) Comparison of adverse events between medications in SNRI overdose and clinical features associated with seizures
(10) Predictors of poisoning severity in single substance diphenhydramine overdoses
(11) Polypharmacy among elderly patients reported to the Toxicology Investigators Consortium
(12) ToxIC QCDR-The First 6 months
(13) Update on prior study of infant poisonings

There were 13 published abstracts from ToxIC presented at various meetings, bringing the total number of published abstracts produced to 120. There were two new full publications from ToxIC in 2018, bringing the total number of papers published since 2010 to 34. These abstracts and publications are listed on the ToxIC website (https://ToxICRegistry.org).

Year 2018 brought the first full year of ToxIC being the vehicle for medical toxicologists to document their compliance with practice quality metrics. Some preliminary information regarding the data collected on these metrics is provided in this annual report.

In addition to the overall summary of ToxIC data presented herein, we present three short sub-analyses that highlight contemporary interest. Because of the prominence of bupropion-induced seizures in current practice we present a more focused view on their occurrence. Similarly, with the consequences of the ever-present opioid epidemic being front and center of medical toxicology practice, and the concomitant rise of addition medicine services provided by medical toxicologists, we are providing our first look at this aspect of our practice. Finally, the third sub-analysis reviews our new ToxIC Qualified Clinical Data Registry.

In October 2018, ToxIC partnered with the National Drug Early Warning System (NDEWS) to develop a capability to identify emerging drugs and drug trends encountered by medical toxicologists during patient consultations and toxicology evaluations. NDEWS monitors emerging drug use trends from a number of sources including medical examiners, the DEA, and regional epidemiologists and disseminates this information through their website and a variety of publications. Reports about new and emerging exposures cared for by ToxIC investigators will now be disseminated in part through NDEWS as part of their ToxIC Briefs. The first two ToxIC Briefs were published in late 2018:

Issue 1: Overview of the Toxicology Investigators Consortium and ToxIC Brief
Issue 2: Novel Synthetic Opioids Cases Reported to the ToxIC Registry, August–October 2018.

ToxIC continues to be supported by funds from the US National Institutes of Health, the US Food and Drug Administration, and a corporate contract with BTG International.

Ongoing investigator-initiated research projects can be found on the ToxIC website.

This ninth ToxIC Annual Report summarizes the main points of the data collected in our main Registry in 2018. Data from the sub-Registries are published separately.

Methods

The procedures and methods for the data collection in the ToxIC Registry have been described in detail [1]. One major change in ToxIC's operating procedures in 2018 was the recruitment of an additional full time staff member to enhance our Quality Assurance program. Currently, all new ToxIC entries are scrutinized in detail and any inconsistences or missing fields are now quickly clarified by communication with the ToxIC investigator entering the case.

Agent entries in primary tables were included for substances with four or more occurrences. Agents with fewer occurrences were listed together under 'miscellaneous.'

The ToxIC Registry operates pursuant to review by the Western Institutional Review Board (IRB) and the IRBs of participating sites.

Results

In 2018, there were a total of 7043 cases reporting toxicologic exposures to the ToxIC Registry. This is a decrease from the prior 6 years as several sub-optimally performing sites were discontinued. Table 1 lists all individual sites that contributed cases in 2018.

Demographics

Tables 2 and 3 summarize selective demographics including age and gender and race and ethnicity, respectively. In 2018, 51.5% of cases involved female patients, 0.6% involved transgender patients (23 female-to-male, 17 male-to-female, 1 unknown). Sixty-eight patients (1%) were pregnant. Age distribution was similar to previous years [1, 2]. The majority of patients were adults aged 19–65 (61.0%) followed by adolescents aged 13–18 (20.3%). Children (≤ 12 years of age) made up 12.5% of cases.

The most commonly reported race was Caucasian (57.5%), followed by Black/African (13.0%) and Asian (3.8%). Race was reported as unknown/uncertain in 21.2% of cases, similar to the previous 2 years [1, 2]. Hispanic ethnicity was reported in 11.5% of cases, and 21.5% of cases reported ethnicity as unknown/uncertain. Race and ethnicity are self-reported by patients, or in cases in which a patient is unable to report, it may be reported by the examining medical toxicologist to the best of their ability.

Table 4 details the referral source of inpatient and outpatient medical toxicology encounters. The majority (58.0%) of inpatient cases were generated by the Emergency Department, and very few cases (0.3%) were referred from Poison Centers. Outpatient encounters were primarily referred by primary care and other outpatient physicians (65.9%), followed by self-referrals (11.6%). These trends were similar to previous years; however, the overall percent of self-referrals decreased by more than half this year compared to recent years [1, 2].

Tables 5 and 6 describe the reason for the toxicology encounter and the details of intentional pharmaceutical exposures, respectively. Consistent with previous years [1, 2], intentional pharmaceutical exposures were the most common reason for medical toxicology encounters (52.4%). Addiction medicine consult was a new reason for encounter in 2018 (2.7%). Within the intentional pharmaceutical exposures, the majority of cases were again an attempt at self-harm (66.7%), primarily suicide attempts (86.1%).

Agent Classes

In 2018, of the 7043 cases entered into the ToxIC Registry, 1949 (27.7%) cases involved multiple agents for a total of 9305 individual agent entries. Consistent with previous years [1, 2], the non-opioid analgesic class was the most common (15.2%), followed by the antidepressant (11.4%), opioid (10.9%), and sedative hypnotic/muscle relaxant (8.6%) classes. Table 7 details the contribution of each agent class to the Registry. Photosensitizing agents represented a new class in 2018 with 1 entry (0%).

Elderly Agent Classes

Table 8 presents the agent classes by age group for older adults. There were 329 cases (4.7%) reporting 509 individual agents of exposure in adults > 65 years of age. A total of 113 (34.3%) cases had more than one agent reported. There were 187 (56.8%) women and no transgender cases reported. The top three agent classes were cardiovascular (14.5%), analgesic (12.4%), and sedative hypnotic/muscle relaxant (10.0%). By age category, the most common exposures by agent class were analgesics for adults 66–75 years of age, and cardiovascular for adults both 76–85 and > 85 years of age. A total of 22.9% of agents reported in adults > 85 years of age were cardiovascular drugs. Also, significant in adults > 85 years of age was the sedative hypnotic/muscle relaxant class, responsible for 16.7% of agents reported and the second most common category in this group. Ethanol was the 7th most common agent (7.4%) for adults 66–75 years of age but was not responsible for any cases reported in adults over 75.

Tables 9 and 10 present cases involving elderly adults by intent of exposure. Intentional pharmaceutical exposures (52.3%), followed by unintentional pharmaceutical (11.9%), and intentional non-pharmaceutical (6.1%) exposures were the most common reasons for encounters. Within the intentional pharmaceutical group, attempt at self-harm (41.9%) and therapeutic use (34.9%) were both common. A total of 21.4% of intentional pharmaceutical encounters in the cardiovascular class were due to therapeutic use.

Individual Agents by Class

Analgesics

Table 11 presents the non-opioid analgesics, the largest class in the Registry. Acetaminophen was again the most commonly reported agent (58.2%), followed by ibuprofen (12.9%), and aspirin (11.7%). Ibuprofen overtook aspirin as the second most commonly reported agent for the first time this year [1–8]. Gabapentin and pregabalin together made up 11% of the class.

Table 1 Participating institutions providing cases to ToxIC in 2018

Arizona
Phoenix
  Banner- University Medical Center Phoenix
  Phoenix Children's Hospital
California
Loma Linda
  Loma Linda University Medical Center
Los Angeles
  Keck Medical Center of USC
  University of Southern California Verdugo Hills
Sacramento
  University of California Davis Medical Center
San Diego
  Rady Children's Hospital
  Scripps Mercy Hospital
  University of California San Diego-Hillcrest
San Francisco
  San Francisco General Hospital
Colorado
Denver
  Colorado Children's Hospital
  Denver Health Medical Center
  Porter and Littleton Hospital
  Swedish Hospital
  University of Colorado Medical Center
Connecticut
Hartford
  Hartford Hospital
Georgia
Atlanta
  Children's Healthcare of Atlanta Egelston
  Children's Healthcare of Atlanta Hughes Spalding
  Emory University Hospital
  Grady Health System
  Grady Memorial Hospital
Illinois
Evanston
  Evanston North Shore University Health System
Indiana
Indianapolis
  IU-Eskenazi Hospital
  IU-Indiana University Hospital
  IU-Methodist Hospital-Indianapolis
  IU-Riley Hospital for Children
Kentucky
Lexington
  University of Kentucky Chandler Medical Center
Massachusetts
Boston
  Beth Israel Boston
  Boston Children's Hospital
Worcester
  University of Massachusetts Memorial Medical Center
Michigan
Grand Rapids
  Spectrum Health Hospitals
Missouri
Kansas City
  Children's Mercy Hospitals & Clinics
St. Louis
  Washington University School of Medicine in St Louis
Nebraska
Omaha
  University of Nebraska Medical Center
New York
Albany
  Albany Medical Center
New York
  Bellevue Medical Center
  NYU Langone Medical Center
Staten Island
  Staten Island University Hospital
Rochester
  Highland Hospital
  Strong Memorial Hospital
Syracuse
  Upstate Medical University-Downtown Campus
North Carolina
Charlotte
  Carolinas Medical Center
Ohio
Cleveland
  Cleveland VA Medical Center
Oregon
Portland
  Doernbecher Children's Hospital
  Oregon Health & Science University Hospital
Pennsylvania
Allentown
  Lehigh Valley Hospital Cedar Crest
  Lehigh Valley Hospital Muhlenberg
  Lehigh Valley-17th Street
Philadelphia
  Hahnemann University Hospital
  Mercy Fitzgerald Hospital
  Mercy Hospital of Philadelphia
  St. Christopher's Hospital for Children
Pittsburgh
  UPMC Children's Hospital of Pittsburgh
  UPMC Magee Women's Hospital
  UPMC Mercy Hospital
  UPMC Presbyterian/Shadyside
South Carolina
Greenville
  Vidant Medical Center
Texas
Dallas
  Children's Medical Center Dallas
  Parkland Memorial Hospital
  University of Texas Southwestern Clinic
  William P Clements University Hospital
Houston
  Ben Taub General Hospital
  Texas Children's Hospital
Utah
Salt Lake City
  Primary Children's Hospital
  University of Utah Hospital
Virginia
Charlottesville
  University of Virginia Health Systems
Richmond
  Virginia Commonwealth University Medical Center
Wisconsin
Milwaukee
  Froedtert Memorial Lutheran Hospital
Israel
Haifa

Table 1 (continued)

New Jersey	Rambam Health Care Campus
New Brunswick	Thailand
Robert Wood Johnson University Hospital	Bangkok
Newark	Vajira Hospital
NJMS/Rutgers	
New Mexico	
Albuquerque	
University of New Mexico	

Antidepressants

Table 12 describes the antidepressant class. The other antidepressant category, driven primarily by bupropion (23.2%) and trazodone (13.6%), was the most frequent category among the antidepressants, similar to previous years [1, 2]. Frequency in reporting of SSRIs, TCAs, and SNRIs was also consistent with previous years' trends [1, 2].

Opioids

Table 13 describes the opioid class. Heroin was again the most common agent in the class, with its contribution increasing to 37.9% in 2018, up from 28.9% in 2017 [1]. Fentanyl was the third most common agent, making up 10.1% of the class, also increased from 2017. Other opioid agents remained fairly stable compared to prior years.

Table 2 ToxIC case demographics—age and gender

	N (%)
Gender	
Male	3377 (47.9)
Female	3624 (51.5)
Transgender	
Female to Male	23 (0.3)
Male to Female	17 (0.2)
Transgender unspecified	1 (< 0.1)
Unknown	1 (< 0.1)
Pregnant	68 (1.0)
Age (years)	
< 2	276 (3.9)
2–6	385 (5.5)
7–12	218 (3.1)
13–18	1427 (20.3)
19–65	4293 (61.0)
66–89	401 (5.7)
> 89	18 (0.3)
Unknown	25 (0.4)
Total	7043 (100)

Sedative Hypnotics

Table 14 presents the sedative hypnotic/muscle relaxant class. Benzodiazepines (primarily alprazolam (21.0%) and clonazepam (15.1%)) and muscle relaxants (primarily baclofen (11.2%) and cyclobenzaprine (10.7%)) were the most common subtypes, similar to previous years [1, 2]. Z-drugs, other sedatives, and barbiturates were again less common.

Anticholinergic/Antihistamine

Table 15 describes the anticholinergic/antihistamine class. Consistent with previous years [1, 2], diphenhydramine (49.8%), followed by hydroxyzine (15.1%), remained the most commonly reported agents in this class.

Sympathomimetics

Table 16 presents the sympathomimetic class. Cocaine (35.1%), followed by methamphetamine (31.6%), and

Table 3 ToxIC case demographics—race and Hispanic ethnicity

	N (%)
Race	
Caucasian	4053 (57.5)
Unknown/uncertain	1495 (21.2)
Black/African	915 (13.0)
Asian	269 (3.8)
Mixed	208 (3.0)
American Indian/Alaska Native	73 (1.0)
Other	20 (0.3)
Native Hawaiian or Pacific Islander	7 (0.1)
Blank	3 (< 0.1)
Total	7043 (100)
Hispanic ethnicity[a]	
Hispanic	813 (11.5)
Non-Hispanic	4717 (67.0)
Unknown	1513 (21.5)
Total	7043 (100)

[a] Hispanic ethnicity as indicated exclusive of race

One case not recorded as Hispanic or non-Hispanic ethnicity

Table 4 ToxIC registry case referral sources by inpatient/outpatient status

	N (%)
Emergency Department (ED) or inpatient (IP)[a]	
ED	3937 (58.0)
Admitting service	1807 (26.6)
Outside hospital transfer	565 (8.3)
Request from another hospital service (not ED)	365 (5.4)
Self-referral	88 (1.3)
Poison Center	17 (0.3)
Primary care provider or other outpatient treating physician	5 (0.1)
Employer/Independent medical evaluation	1 (< 0.1)
ED/IP total	6785 (100)
Outpatient (OP)/clinic/office consultation[b]	
Primary care provider or other OP physician	170 (65.9)
Self-referral	30 (11.6)
Employer/Independent medical evaluation	26 (10.1)
Poison Center	12 (4.7)
ED	11 (4.3)
Admitting service	4 (1.6)
Request from another hospital service (not ED)	4 (1.6)
Outside hospital transfer	1 (0.4)
OP total	258 (100)

[a] Percentage based on the total number of cases ($N = 6785$) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP)

[b] Percentage based on the total number of cases ($N = 258$) seen by a medical toxicologist as outpatient, clinic visit, or office consultation

amphetamine (11.1%) were the most commonly reported agents in the class again this year.

Toxic Alcohol and Ethanol

Table 17 describes data on ethanol and toxic alcohols. Ethanol was considered its own agent class, consistent with prior years and was the seventh most commonly reported agent class. The most commonly reported nonethanol alcohols and glycols were ethylene glycol and isopropanol, together making up 64.8% of the agent class. There were a number of miscellaneous alcohols and glycols reported which together made up 22.5% of the class.

Cardiovascular Agents

Table 18 shows data on the cardiovascular class. For the second consecutive year in the Registry, sympatholytics (26.3%) outnumber beta-blockers (24.3%) as the most common subclass of cardiovascular agents, followed by calcium channel blockers (15.4%) [1]. Clonidine (21.4%) and metoprolol (12.9%) were the most common sympatholytic and beta-blocker agents, respectively, and the two most common agents reported to the overall class. Vasodilators/other antihypertensives, ACEI and ARBs, antidysrhythmics and other cardiovascular agents, and cardiac glycosides each accounted for less than 10% of the class.

Older Adult Cardiovascular Agents

Table 19 describes the cardiovascular agents reported in cases of age > 65. Metoprolol (21.6%) and digoxin (20.3%) were the most commonly reported agents, followed by amlodipine (9.5%).

Antipsychotics

Table 20 details the antipsychotic class. Trends in the antipsychotic class were similar to previous years, with the atypicals, led by quetiapine (46.1%) and olanzapine (15.9%), representing the majority of cases reported [1, 2].

Anticonvulsants, Mood Stabilizers, and Lithium

Table 21 presents data on anticonvulsants, mood stabilizers, and lithium. Consistent with past years, lithium was considered as its own agent class and made up just over 1% of reported agents in the Registry. Among anticonvulsants and

Table 5 Reason for medical toxicology encounter

	N (%)
Intentional exposure-pharmaceutical	3690 (52.4)
Intentional exposure-non-pharmaceutical	775 (11.0)
Unintentional exposure-pharmaceutical	587 (8.3)
Unintentional exposure-non-pharmaceutical	319 (4.5)
Organ system dysfunction	318 (4.5)
Envenomation-snake	239 (3.4)
Addiction medicine consultation	190 (2.7)
Withdrawal-ethanol	167 (2.4)
Withdrawal-opioid	165 (2.3)
Interpretation of toxicology lab data	131 (1.9)
Environmental evaluation	115 (1.6)
Ethanol abuse	89 (1.2)
Occupational evaluation	84 (1.2)
Withdrawal-sedative/hypnotic	47 (0.7)
Envenomation-spider	41 (0.6)
Malicious/criminal	32 (0.5)
Envenomation-other	19 (0.3)
Blank	13 (0.2)
Withdrawal-other	11 (0.2)
Envenomation-scorpion	6 (0.1)
Marine/fish poisoning	3 (< 0.1)
Withdrawal-cocaine/amphetamine	2 (< 0.1)
Total	7043 (100)

mood stabilizers, lamotrigine and valproic acid were the most commonly reported, together making up almost half (47%) of the class. Similar to past years, carbamazepine and topiramate were the next most common, contributing 10.2% and 9.8%, respectively.

Table 6 Detailed reason for encounter-intentional pharmaceutical exposure

	N (%)
Reason for intentional pharmaceutical exposure subgroup[a]	
Attempt at self-harm	2463 (66.7)
Misuse/abuse	627 (17.0)
Therapeutic use	291 (7.9)
Unknown	309 (8.4)
Total	3690 (100)
Attempt at self-harm- suicidal intent subclassification[b]	
Suicidal intent	2121 (86.1)
Suicidal intent unknown	253 (10.3)
No suicidal intent	85 (3.5)
Not recorded	4 (0.2)
Total	2463 (100)

[a] Percentage of total number of cases ($N = 3690$) indicating primary reason for encounter due to intentional pharmaceutical exposure

[b] Percentage of number of cases indicating attempt at self-harm ($N = 2463$)

Table 7 Agent classes involved in medical toxicology consultation

	N (%)[a]
Analgesic	1411 (15.2)
Antidepressant	1057 (11.4)
Opioid	1010 (10.9)
Sedative-hypnotic/muscle relaxant	803 (8.6)
Anticholinergic/antihistamine	608 (6.5)
Sympathomimetic	581 (6.2)
Ethanol	568 (6.1)
Cardiovascular	561 (6.0)
Antipsychotic	440 (4.7)
Anticonvulsant	325 (3.5)
Envenomation and marine	274 (2.9)
Psychoactive	260 (2.8)
Diabetic medication	141 (1.5)
Cough and cold products	116 (1.2)
Lithium	112 (1.2)
Gases/irritants/vapors/dusts	111 (1.2)
Herbal products/dietary supplements	110 (1.2)
Metals	101 (1.1)
Hydrocarbon	73 (0.8)
Caustic	70 (0.8)
Household products	65 (0.7)
Antimicrobials	63 (0.7)
Plants and fungi	58 (0.6)
Unknown	52 (0.6)
GI	39 (0.4)
Anticoagulant	31 (0.3)
Endocrine	25 (0.3)
Chemotherapeutic and immune	24 (0.3)
Other nonpharmaceutical product	24 (0.3)
Other pharmaceutical product	24 (0.3)
Anesthetic	23 (0.2)
Insecticide	21 (0.2)
Rodenticide	11 (0.1)
Anti-parkinsonism drugs	9 (0.1)
Herbicide	7 (0.1)
Ingested foreign body	6 (0.1)
Pulmonary	6 (0.1)
Amphetamine-like hallucinogen	5 (0.1)
WMD[b]/riot agent/radiological	5 (0.1)
Fungicide	3 (< 0.1)
Photosensitizing agent	1 (< 0.1)
Unknown agent	62 (0.6)
Total	9305 (100)

[a] Percentages are out of total number of reported agent entries in 2018; 1949 cases (27.7%) reported multiple agents

[b] *WMD* weapons of mass destruction

Table 8 ToxIC 2018–Agent classes for older adult cases

	Exposure rank	Totals	%[a]	Age 66–75	Age 76–85	Age > 85
Cardiovascular	1	74	14.5%	37	26	11
Analgesic	2	63	12.4%	38	18	7
Sedative-hypnotic/muscle relaxant	3	51	10.0%	31	12	8
Antidepressant	4	45	8.8%	19	21	5
Opioid	5	43	8.4%	32	7	4
Diabetic Med	6	26	5.1%	15	10	1
Ethanol	7	24	4.7%	24	0	0
Anticholinergic/antihistamine	8	20	3.9%	12	5	3
Envenomation	8	20	3.9%	13	6	1
Antipsychotic	9	16	3.1%	13	3	0
Anticonvulsant	10	13	2.6%	11	2	0
Metals	11	11	2.2%	7	3	1
Toxic alcohols	12	10	2.0%	9	1	0
Antimicrobials	13	9	1.8%	7	2	0
Sympathomimetic	13	9	1.8%	8	1	0
Caustic	14	7	1.4%	6	0	1
Lithium	14	7	1.4%	5	2	0
Anticoagulant	13	6	1.2%	2	3	1
Gases/vapors/irritants/dusts	13	6	1.2%	5	1	0
Household	13	6	1.2%	5	1	0
Other pharmaceutical	12	5	1.0%	4	0	1
Parkinson's Med	12	5	1.0%	1	3	1
Plants/fungi	12	5	1.0%	2	3	0
Anesthetic	11	4	0.8%	2	1	1
GI agent	10	3	0.6%	3	0	0
Hydrocarbon	10	3	0.6%	3	0	0
Other nonpharmaceuticals	10	3	0.6%	2	1	0
Unknown class	10	3	0.6%	2	1	0
Chemotherapeutic and immune	9	2	0.4%	0	1	1
Endocrine	9	2	0.4%	2	0	0
Herbals/dietary supplements/vitamins	9	2	0.4%	2	0	0
Psychoactive	9	2	0.4%	0	2	0
Cough and cold	8	1	0.2%	1	0	0
Herbicide	8	1	0.2%	1	0	0
Insecticide	8	1	0.2%	0	0	1
Pulmonary	8	1	0.2%	1	0	0
Totals		509	100.0%			

[a] Percentages are out of total number of reported agent entries per year; 113 cases (34.3%) reported multiple agents

Envenomations and Marine Poisonings

Table 22 shows data on envenomations and marine poisonings. Snake envenomations represented by *Crotalus* (38%), *Agkistrodon* (17.2%), and snake unspecified (16.4%) composed the top three exposures reported to this class. This trend differs from last year when *Agkistrodon* species slightly outnumbered Crotalus [1]. Again in 2018, *Loxosceles* exposures were the 4th most common exposure in this class (8.4%).

Psychoactives

Table 23 presents data on the psychoactive class including the amphetamine-like hallucinogen methylenedioxymethamphetamine (Molly). In 2017, an

Table 9 Reason for medical toxicology encounter older adults

	N (%)
Intentional exposure-pharmaceutical	172 (52.3)
Unintentional exposure-pharmaceutical	39 (11.9)
Intentional exposure–non-pharmaceutical	20 (6.1)
Envenomation-snake	17 (5.2)
Organ system dysfunction	17 (5.2)
Unintentional exposure-non-pharmaceutical	14 (4.3)
Environmental evaluation	12 (3.6)
Withdrawal-ethanol	9 (2.7)
Interpretation of toxicology lab data	8 (2.4)
Addiction medicine consultation	6 (1.8)
Withdrawal-opioids	5 (1.5)
Ethanol abuse	3 (0.9)
Envenomation-other	1 (0.3)
Envenomation-scorpion	1 (0.3)
Envenomation-spider	1 (0.3)
Malicious/criminal	1 (0.3)
Occupational evaluation	1 (0.3)
Withdrawal-other	1 (0.3)
Withdrawal–sedative hypnotics	1 (0.3)
Total	329 (100)

increase in Molly cases was noted (6 to 12 from the previous year) [1] which decreased in 2018, with five cases reported. Similar to last year, marijuana cases (36.5%) again surpassed synthetic cannabinoid cases (12.3%). This trend is a reversal to findings from 2015 to 2016 when synthetic cannabinoid cases were more prevelant [1, 2, 5]. This proportional increase of marijuana cases was even more pronounced this year. Additionally in

Table 10 Detailed reason for encounter-intentional pharmaceutical exposure in older adults

	N (%)
Reason for intentional pharmaceutical exposure subgroup[a]	
Attempt at self-harm	72 (41.9)
Therapeutic use	60 (34.9)
Misuse/abuse	24 (14.0)
Unknown	16 (9.3)
Total	172 (100)
Attempt at self-harm- suicidal intent subclassification[b]	
Suicidal intent	60 (83.3)
Suicidal intent unknown	11 (15.3)
No suicidal intent	1 (1.4)
Total	72 (100)

[a] Percentage of total number of cases ($N = 172$) indicating primary reason for encounter due to intentional pharmaceutical exposure

[b] Percentage of number of cases indicating attempt at self-harm ($N = 72$)

Table 11 Analgesics

	N (%)
Acetaminophen	821 (58.2)
Ibuprofen	182 (12.9)
Aspirin	165 (11.7)
Gabapentin	134 (9.5)
Naproxen	36 (2.6)
Pregabalin	21 (1.5)
Salicylic acid	21 (1.5)
Analgesic unspecified	11 (0.8)
Meloxicam	6 (0.4)
Miscellaneous[a]	14 (1.0)
Class total	1411 (100)

[a] Includes aminophenazone, etodolac, diclofenac, methylsalicylate, phenazopyridine, salsalate, and unspecified NSAID

2018, non-synthetic cannabinoids (12.7%) became the second most common agent reported for the first time in Registry history, doubling in frequency from the previous

Table 12 Antidepressants

	N (%)
Other antidepressants	452 (42.8)
Bupropion	245 (23.2)
Trazodone	144 (13.6)
Mirtazapine	31 (2.9)
Antidepressant unspecified	23 (2.2)
Vilazodone	5 (0.5)
Miscellaneous[a]	< 5 (< 0.4)
Selective serotonin reuptake inhibitors (SSRIs)	380 (36.0)
Sertraline	130 (12.3)
Fluoxetine	95 (9.0)
Escitalopram	69 (6.5)
Citalopram	64 (6.1)
Miscellaneous[b]	< 5 (< 0.4)
Tricyclic antidepressants (TCAs)	123 (11.6)
Amitriptyline	81 (7.7)
Doxepin	21 (2.0)
Nortriptyline	17 (1.6)
Miscellaneous[c]	< 5 (< 0.4)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	102 (9.6)
Venlafaxine	67 (6.3)
Duloxetine	31 (2.9)
Miscellaneous[d]	< 5 (< 0.4)
Class total	1057 (100)

[a] Includes vortioxetine, tranylcypromine

[b] Includes fluvoxamine

[c] Includes imipramine, clomipramine, desipramine

[d] Includes desvenlafaxine

Table 13 Opioids

	N (%)
Heroin	383 (37.9)
Oxycodone	125 (12.4)
Fentanyl	102 (10.1)
Tramadol	82 (8.1)
Buprenorphine	62 (6.1)
Methadone	57 (5.6)
Opioid unspecified	57 (5.6)
Hydrocodone	46 (4.6)
Morphine	31 (3.1)
Loperamide	12 (1.2)
Hydromorphone	11 (1.1)
Codeine	10 (1.0)
Naloxone	9 (0.9)
Miscellaneous[a]	23 (2.3)
Class total	1010 (100)

[a] Includes acetyl fentanyl, butorphanol, depropionylfentanyl, diphenoxylate, fluoroisobutyryl fentanyl (4- or para-), methyl norfentanyl, N-allyl norfentanyl, naltrexone, norfentanyl, oxymorphone, remifentanil, tapentadol, U47700

year [1–5]. Reported cases of nicotine and cannabidiol also increased this year. Overall, the number of psychoactive cases reported increased this year compared to 2017 [1].

Diabetic Agents

Table 24 presents the diabetic medication agent class. Metformin was the most common agent at 32.6% of the agent class. The sulfonylureas glipizide, glimepiride, and glyburide together made up 34% of the class.

Gases, Irritants, Vapors, and Dusts

Table 25 describes the gases, irritants, vapors, and dusts class. Carbon monoxide was again the most common reported agent in this class (65.8%) [1–5], followed by smoke (6.3%) and chlorine (4.5%) gases.

Metals

Table 26 presents the metal class. Lithium is its own agent class, reported here with the anticonvulsants and mood stabilizers. Trends were similar to previous years with lead (26.7%) and iron (24.8%) representing the majority of reported cases. Notably, there was not an increase in reported cases of lead in 2018 compared to the previous 3 years [1, 2, 5]. Gadolinium (10.9%) cases increased in 2018.

Table 14 Sedative-hypnotic/muscle relaxants by type

	N (%)
Benzodiazepines	426 (53.1)
Alprazolam	169 (21.0)
Clonazepam	121 (15.1)
Lorazepam	60 (7.5)
Benzodiazepine unspecified	29 (3.6)
Diazepam	29 (3.6)
Chlordiazepoxide	7 (0.9)
Temazepam	6 (0.7)
Miscellaneous[a]	5 (0.6)
Muscle Relaxants	234 (29.1)
Baclofen	90 (11.2)
Cyclobenzaprine	86 (10.7)
Tizanidine	28 (3.5)
Carisoprodol	16 (2.0)
Methocarbamol	10 (1.2)
Miscellaneous[b]	4 (0.5)
Non-benzodiazepine agonists (“Z” drugs)	59 (7.3)
Zolpidem	51 (6.4)
Eszopiclone	6 (0.7)
Zaleplon	2 (0.2)
Other sedatives	58 (7.2)
Buspirone	24 (3.0)
Sed-hypnotic/muscle relaxant unspecified	17 (2.1)
Miscellaneous[c]	17 (2.1)
Barbiturates	26 (3.2)
Butalbital	14 (1.7)
Phenobarbital	6 (0.7)
Miscellaneous[d]	6 (0.7)
Class total	803 (100)

[a] Includes clorazepate, lorazepam, and triazolam

[b] Includes cisatracurium and metaxalone

[c] Includes acepromazine, aminobutyric acid, etizolam, flumazenil, methaqualone, orphenadrine, propofol, phenibut, ramelteon, and suvorexant

[d] Includes butabarbital, pentobarbital, and secobarbital

Herbal Products and Dietary Supplements

Table 27 details herbal products and dietary supplements. Caffeine was again the most commonly reported agent. Infrequently reported miscellaneous agents made up 33.6% of the agent class.

Household Agents

Table 28 describes household agents reported to the Registry. Cleaning solutions and disinfectants (29.2%), sodium hypochlorite $\leq$ 6% (18.5%), and laundry detergent pods (15.4%)

Table 15 Anticholinergics and antihistamines

	N (%)
Diphenhydramine	303 (49.8)
Hydroxyzine	92 (15.1)
Doxylamine	35 (5.6)
Promethazine	28 (4.6)
Benztropine	26 (4.3)
Anticholinergic unspecified	24 (3.9)
Chlorpheniramine	24 (3.9)
Loratadine	13 (2.1)
Dicyclomine	11 (1.8)
Certirizine	9 (1.5)
Trihexyphenidyl	8 (1.3)
Antihistamine unspecified	7 (1.1)
Meclizine	5 (0.8)
Pyrilamine	5 (0.8)
Miscellaneous[a]	18 (3.0)
Class total	608 (100)

[a] Includes brompheniramine, oxybutynin, scopolamine, atropine, cyproheptadine, dimenhydrinate, fexofenadine, glycopyrrolate, hyoscyamine, mirabegron, and tiotropium

were the top three most commonly reported agents in this class. The relative contribution of laundry pod exposures increased in 2018 after a small decrease last year (11.8%) [1].

Table 16 Sympathomimetic agents

	N (%)
Cocaine	203 (35.1)
Methamphetamine	183 (31.6)
Amphetamine	64 (11.1)
Methylphenidate	31 (5.4)
Dextroamphetamine	22 (3.8)
Lisdexamfetamine	17 (2.9)
MDMA (Methylenedioxy-N-methamphetamine, Ecstasy)	14 (2.4)
Sympathomimetic unspecified	11 (1.9)
Phentermine	7 (1.2)
Atomoxetine	4 (0.7)
Dexmethylphenidate	4 (0.7)
Pseudoephedrine	4 (0.7)
Clenbuterol	3 (0.5)
Miscellaneous[a]	12 (2.1)
Class total	579 (100)

[a] Includes 2,5-dimethoxy-4-bromophenethylamine, 25-NBOMe, α-pyrrolidinohexiophenone.(α-PHP), cathinone, diethylpropion, ephedrine, epinephrine, phenmetrazine, phenylephrine, phenylethylamine, propylhexedrine, and tetrahydrozoline

Table 17 Ethanol and toxic alcohols

	N (%)
Ethanol[a]	568 (100)
Nonethanol alcohols and glycols	
Ethylene glycol	25 (35.2)
Isopropanol	21 (29.6)
Methanol	9 (12.7)
Miscellaneous[b]	16 (22.5)
Class total	71 (100)

[a] Ethanol is considered a separate agent class

[b] Includes butanol, ethylene glycol monohexyl, diethyl ether, diethylene glycol, glycol ethers, and toxic alcohol unspecified

Plants and Fungi

Table 29 presents data for plant and fungi exposures for the Registry in 2018. Trends were unchanged from the previous year with mold representing the most common exposure (41.4%), followed by mushroom unknown/unspecified (17.2%) and Mitragyna speciosa (kratom) (12.1%) exposures. Infrequent miscellaneous agents made up 29.3% of the class.

Supplemental Tables

Cough and Cold Preparations

Table S1 details data on cough and cold preparations reported to the Registry. Dextromethorphan was by far the most commonly reported agent, making up 87.1% of the class.

Hydrocarbons

Table S2 presents the hydrocarbon agent class. The largest contributor to the class was unspecified hydrocarbons with 31.5% of the agent class. Methane was the next most commonly reported making up 8.2% of the class.

Caustics

Table S3 presents the caustic agent class. Hydrofluoric acid was the most common agent reported in 2018 making up 14.3% of the class, an increase from the past 2 years [1, 2]. Less frequently reported miscellaneous agents made up nearly half of the agent class (48.6%).

Antimicrobials

Table S4 presents data on antimicrobial agents which is subdivided into antibiotics, antivirals, and other antimicrobial agents. In 2018, dapsone was the most commonly reported agent (12.7%). Antiviral agents made up 15.9% of the class

Table 18 Cardiovascular agents by type

	N (%)
α_2 Agonists	147 (26.3)
Clonidine	120 (21.4)
Guanfacine	26 (4.6)
Xylazine	1 (0.2)
Beta blockers	136 (24.3)
Metoprolol	72 (12.9)
Propranolol	32 (5.7)
Atenolol	15 (2.7)
Carvedilol	13 (2.3)
Miscellaneous[a]	4 (0.7)
Calcium channel blockers	86 (15.4)
Amlodipine	45 (8.0)
Diltiazem	20 (3.6)
Verapamil	15 (2.7)
Miscellaneous[b]	6 (1.1)
Other antihypertensives and vasodilators	55 (9.8)
Prazosin	28 (5.0)
Antihypertensive unspecified	11 (2.0)
Isosorbide	6 (1.1)
Hydralazine	5 (0.9)
Miscellaneous[c]	5 (0.9)
ACEI/ARB	51 (9.1)
Lisinopril	35 (6.2)
Losartan	10 (1.8)
Miscellaneous[d]	6 (1.1)
Antidysrhythmics and other cardiovascular agents	26 (4.6)
Cardiovascular agent unspecified	11 (2.0)
Amiodarone	5 (0.9)
Sotalol	5 (0.9)
Miscellaneous[e]	5 (0.9)
Cardiac glycosides	24 (4.3)
Digoxin	23 (4.1)
Digitoxin	1 (0.2)
Diuretics	22 (3.9)
Hydrochlorothiazide	7 (1.2)
Furosemide	6 (1.1)
Miscellaneous[f]	9 (1.6)
Antihyperlipidemic	13 (2.3)
Atorvastatin	8 (1.4)
Miscellaneous[g]	5 (0.9)
Class total	560 (100)

[a] Includes bisoprolol, nadolol, and nebivolol

[b] Includes lercanidipine and nifedipine

[c] Includes nitroglycerin, nitroprusside, pentoxifylline, phentolamine, and tamsulosin

[d] Includes enalapril and valsartan

[e] Includes dofetilide and flecainide

[f] Includes acetazolamide, bumetanide, chlorthalidone, spironolactone, and triamterene

[g] Includes lovastatin, rosuvastatin, and simvastatin

and were predominantly miscellaneous agents (11.1%). The other antimicrobial subsection was made up of multiple miscellaneous agents (15.9%).

Endocrine

Table S5 describes the 25 endocrine agents reported. Levothyroxine represents the majority (56.0%) of the cases reported in this class.

Chemotherapeutic and Immunological Agents

Table S6 describes chemotherapeutic and immunological agents. Hydroxychloroquine (25%), methotrexate (16.7%), and colchicine (16.7%) were the three most commonly reported agents. Relative hydroxychloroquine exposures increased from 2017 [1].

Other Non-pharmaceuticals

Table S7 describes the other non-pharmaceutical class. Methacrylates (20.8%) were the most common agents in this class. Miscellaneous agents made up 50.0% of this class.

Table 19 Most frequent agent exposures in cardiovascular class age > 65

	N (%)[a]
Metoprolol	16 (21.6)
Digoxin	15 (20.3)
Amlodipine	7 (9.5)
Amiodarone	4 (5.4)
Diltiazem	4 (5.4)
Atenolol	3 (4.1)
Lisinopril	3 (4.1)
Verapamil	3 (4.1)
Carvedilol	2 (2.7)
Flecainide	2 (2.7)
Isosorbide	2 (2.7)
Propranolol	2 (2.7)
Sotalol	2 (2.7)
Atorvastatin	1 (1.4)
Clonidine	1 (1.4)
Enalapril	1 (1.4)
Hydralazine	1 (1.4)
Lercanidipine	1 (1.4)
Nadolol	1 (1.4)
Nebivolol	1 (1.4)
Nifedipine	1 (1.4)
Tamsulosin	1 (1.4)
Class total	74 (100)

[a] Percentages are out of total number of cardiovascular agent exposures reported in adults aged > 65 in 2018 ($N = 74$)

Table 20 Antipsychotics

	N (%)
Quetiapine	203 (46.1)
Olanzapine	70 (15.9)
Risperidone	42 (9.5)
Aripiprazole	41 (9.3)
Haloperidol	24 (5.5)
Antipsychotic unspecified	10 (2.3)
Lurasidone	10 (2.3)
Ziprasidone	8 (1.8)
Clozapine	7 (1.6)
Paliperidone	6 (1.4)
Miscellaneous[a]	19 (4.3)
Class total	440 (100)

[a] Includes chlorpromazine, fluphenazine, prochlorperazine, brexpiprazole, amisulpride, asenapine, cariprazine, loxapine, perphenazine, and thioridazine.

Gastrointestinal Agents

Table S8 presents gastrointestinal agents. Omeprazole (27.5%), ondansetron (22.5%), and ranitidine (20.0%) were the most commonly reported agents.

Insecticides, Herbicides, Rodenticides, and Fungicides

Table S9 presents the insecticide, herbicide, rodenticide, and fungicide class. There were 21 insecticides reported. Miscellaneous agents composed 38.1% and pyrethrins composed 28.6% of insecticides. There were 11 rodenticides reported. Brodifacoum composed 45.5% of rodenticides. Herbicides and fungicides were infrequently reported.

Table 21 Anticonvulsants and mood stabilizers

	N (%)
Lithium[a]	112 (100)
Lamotrigine	82 (25.2)
Valproic acid	71 (21.8)
Carbamazepine	33 (10.2)
Topiramate	32 (9.8)
Phenytoin	27 (8.3)
Levetiracetam	25 (7.7)
Oxcarbazepine	22 (6.8)
Divalproex	7 (2.2)
Lacosamide	7 (2.2)
Zonisamide	7 (2.2)
Anticonvulsant unspecified	5 (1.5)
Miscellaneous[b]	2 (0.6)
Class total	325 (100)

[a] Lithium is considered a separate agent class

[b] Includes ethosuximide and primidone

Anticoagulants

Table S10 details anticoagulant class exposures. Warfarin was the most commonly reported agent (61.3%).

Other Pharmaceuticals

Table S11 presents the other pharmaceutical products agent class. The majority of the class (70.8%) was made up of infrequently reported miscellaneous agents. Unspecified pharmaceutical products were the most commonly reported agent (16.7%).

Anesthetics

Table S12 describes anesthetic class exposures. There were 23 entries in this class. Benzonatate was the most commonly reported agent.

Weapons of Mass Destruction

Table S13 describes the weapons of mass destruction class. This year botulinum toxin was the only agent in the weapons of mass destruction class reported.

Anti-Parkinsonism Agents

Table S14 presents the anti-parkinsonism agent class, containing nine entries. Levodopa/carbidopa was reported with the most frequency (77.8%). Pramipexole and ropinirole each had one entry.

Foreign Bodies

Table S15 details the six foreign body ingestions reported to the registry in 2018. Batteries represented 50% of foreign body ingestions.

Pulmonary Agents

Table S16 describes reported pulmonary agents. Montelukast was the most common agent reported (50%).

Clinical Signs and Symptoms

The clinical signs and symptoms categories report information on a diverse range of abnormal clinical findings. In order to be reported as being present, predefined criteria must be met for

Table 22 Envenomations and marine poisonings

	N (%)
Crotalus (Rattlesnake)	104 (38.0)
Agkistrodon (Copperhead, Cottonmouth/Water moccasin)	47 (17.2)
Snake unspecified	45 (16.4)
Loxosceles (Recluse spiders)	23 (8.4)
Trimeresurus albolabris (var Pit viper incl white lipped, green tree)	12 (4.4)
Envenomation unspecified	7 (2.6)
Miscellaneous[a]	36 (13.1)
Class Total	274 (100)

[a] Includes *Aspidelaps lubricus* (Coral cobra), *Bitis gabonica* (Gaboon viper), *Chilopoda* (Centipede unspecified), *Ciguetara* poisoning, *Hydrodynastes gigas* (False water cobra), *Hymenoptera spp.*, *Latrodectus* (Widow spiders), *Micrurus* (Eastern coral snake), *Naja kaouthia* (Monocled cobra), palytoxin, *Trimeresurus* unspecified (Pit viper unspecified), *Vipera palaestinae*, unspecified animal bite, unspecified insect, unspecified scorpion, and unspecified spider

each category. For example, tachycardia is defined as a heart rate greater than 140 beats per minute. Additionally, each case may report more than one abnormality within a group or across groups. For example, a single case entry may have multiple vital sign abnormalities, or may have both a vital sign abnormality and a neurologic abnormality. The percentages for these categories are calculated relative to the total number of Registry cases. It is therefore possible for the total to be more than 100%.

Table 23 Psychoactives

	N (%)
Molly-amphetamine-like hallucinogen[a]	5 (100)
Marijuana	95 (36.5)
Cannabinoid nonsynthetic	33 (12.7)
Cannabinoid synthetic	32 (12.3)
Gamma hydroxybutyrate	16 (6.2)
Ketamine	14 (5.4)
LSD	13 (5.0)
Phencyclidine	11 (4.2)
Nicotine	8 (3.1)
Cannabidiol	7 (2.7)
Methylenedioxymethamphetamine	5 (1.9)
Delta-9-tetrahydrocannabinol	5 (1.9)
Miscellaneous[b]	21 (8.1)
Class total	260 (100)

[a] Amphetamine-like hallucinogens are considered a separate agent class

LSD lysergic acid diethylamide

[b] Includes psychoactive unspecified, 1,4-Butanediol, donepezil, 3-methoxyphencyclidine, gamma butyrolactone, tetrahydrocannabinol, 3-Methoxy Eticyclidine (3-MeO PCE), disulfiram, dimethyltryptamine (DMT), Eticyclidine (O-PCE, 2-Oxo-PCE), gutka, hallucinogen unspecified, ibogaine, O-Acetylpsilocin, pharmaceutical tetrahydrocannabinol (THC), piracetam.

Toxidromes

Table 30 reports the 2156 toxidromes reported to the Registry in 2018. Consistent with previous years, the sedative-hypnotic toxidrome was the most common (10.8%). The next top four toxidromes were also unchanged from 2017: anticholinergic (6.6%), sympathomimetic (4.7%), opioid (3.2%), and serotonin syndrome (2.7%) [1].

Major Vital Sign Abnormalities

Table 31 presents the 1974 vital sign abnormalities reported to the Registry in 2018. Trends were similar to the previous year [1]. Tachycardia (11.9%), hypotension (6.9%), and bradycardia (4.2%) were the most common vital sign abnormalities reported.

Clinical Signs and Symptoms—Neurologic

Table 32 describes the 3783 neurologic clinical signs and symptoms. Coma/CNS depression (29.6%), agitation

Table 24 Diabetic medications

	N (%)
Metformin	46 (32.6)
Insulin	36 (25.5)
Glipizide	27 (19.1)
Glimepiride	15 (10.6)
Glyburide	6 (4.3)
Miscellaneous[a]	11 (7.8)
Class total	141 (100)

[a] Includes diabetic medication unspecified, dulaglutide, empagliflozin, gliclazide, sitagliptin, and sulfonylurea unspecified

Table 25 Gases, irritants, vapors, and dusts

	N (%)
Carbon monoxide	73 (65.8)
Smoke	7 (6.3)
Chlorine	5 (4.5)
Gases/vapors/irritants/dusts unspecified	5 (4.5)
Miscellaneous[a]	21 (18.9)
Class total	111 (100)

[a] Includes cyanide, fumes/vapors/gases unspecified, volatile organic compounds (VOC) unspecified, diesel exhaust, dust, nitrogen oxides, chloramine, duster (canned air), exhaust fumes, fiberglass, phosgene, polyurethane vapors.

(14.7%), and delirium/toxic psychosis (10.5%) remained the most commonly reported signs.

Clinical Signs and Symptoms—Cardiovascular and Pulmonary

Table 33 presents the 642 cardiovascular and 849 pulmonary clinical signs reported to the Registry in 2018. QTc (5.1%) and respiratory depression (8.8%) remained the most common signs in their respective categories this year.

Clinical Signs—Other Organ Systems

Table 34 presents the other organ system clinical signs which include metabolic, renal and musculoskeletal, hematological, gastrointestinal and hepatic, and dermatological. Metabolic abnormalities were again the most frequently reported, and among these an elevated anion gap and metabolic acidosis were the most common. Renal and musculoskeletal abnormalities were the next most commonly reported, with acute kidney injury (4.0%) and rhabdomyolysis (3.7%) reported with similar frequencies. Coagulopathy was the most commonly reported hematological abnormality (2.0%). Hepatotoxicity was the most common gastrointestinal and hepatic abnormality (3.1%). Other gastrointestinal and hepatic abnormalities were less common, each reported in less than 1% of total Registry cases. Among cases reporting any clinical sign, dermatological abnormalities were less frequently reported (2.7%), with rash being the most commonly reported among these.

Table 26 Metals

	N (%)
Lead	27 (26.7)
Iron	25 (24.8)
Gadolinium	11 (10.9)
Cadmium	7 (6.9)
Arsenic	5 (5.0)
Cobalt	4 (4.0)
Copper	4 (4.0)
Mercury	4 (4.0)
Metal unspecified	3 (3.0)
Chromium	2 (2.0)
Nickel	2 (2.0)
Miscellaneous[a]	7 (6.9)
Class total	101 (100)

[a] Includes aluminum, antimony, copper sulfate, magnesium, mercuric sulfate, unspecified steel iron, and uranium

Table 27 Herbal products and dietary supplements

	N (%)
Caffeine	42 (38.2)
Melatonin	21 (19.1)
Herbals/dietary supplements/vitamins unspecified	10 (9.1)
Miscellaneous[a]	37 (33.6)
Class total	110 (100)

[a] Includes *Aleurites moluccanus* (candlenut seed), Angelica sinensis (Dong quai, female ginseng), botanical essential oil mixture not otherwise specified, calcium, copaiba (copaifera) extract or oil, dietary supplement unspecified, dinitrophenol, essential oil unspecified, eucalyptus oil, eugenol (clove oil), frankensence (Boswellia) extract or oil, grapefruit extract, herbal (dietary) multibotanical, juniper (Juniperus) extract or oil, methylxanthine, multiple vitamin, peppermint oil, potassium, senna, tea tree oil, tryptophan, vitamin B1 (thiamine), vitamin B3 (niacin), vitamin B12 (cyanocobalamin), vitamin C (ascorbic acid), vitamin D, vitamin unspecified, and yohimbine.

Fatalities

Tables 35 and 36 present cases in which fatalities were reported in 2018. Table 35 includes cases in which a single agent was reported; Table 36 includes cases involving multiple

Table 28 Household products

	N (%)
Cleaning solutions and disinfectants	19 (29.2)
Sodium hypochlorite ≤ 6%	12 (18.5)
Laundry detergent pod	10 (15.4)
Soaps and detergents	9 (13.8)
Miscellaneous[a]	15 (23.1)
Class total	65 (100)

[a] Includes aromatic or essential oils (carrier/solvent base unspecified), dishwasher detergent, enamel/clearcoats, fabric softener, hair product, hand sanitizer unspecified, latex unspecified, paint stripper, perfume, phenylenediamine (hair dye), shaving cream, spray adhesive, windshield washer fluid

Table 29 Plants and fungi

	N (%)
Mold	24 (41.4)
Mushroom, other/unknown	10 (17.2)
Mitragyna speciosa (kratom)	7 (12.1)
Amanita pantherina	2 (3.4)
Lavender	2 (3.4)
Miscellaneous[a]	13 (22.4)
Class Total	58 (100)

[a] Includes *Abrus precatorius* (rosary pea), *Arnica*, betel nut, *Cerbera manghas* (sea mango), *Cerbera odollam* (pong-pong seeds), *Datura stramonium* (jimson weed), *Drimia maritima* (squill), *Mentha pulegium* (pennyroyal), *Ganoderma* mushrooms, psilocybin mushrooms, *Ricinus communis* (castor beans), strychnine, and *Vicia faba* (fava bean)

agents. Table S17 in the Supplementary materials presents those fatalities in which it is unknown whether there was a related toxicologic exposure.

There were 106 fatalities in 2018, comprising 1.5% of Registry cases. The percentage of reported fatalities in 2018 ties 2016 for the most reported fatalities in Registry history [1–5]. 49 cases involved single agent exposures, 34 involved multiple agents, and in 23 cases it was unknown if there was a toxicologic exposure.

There were 36 cases involving opioids, 10 involving fentanyl and 7 as single opioid agents.

Acetaminophen was the most common agent involved in both single and multiple agent fatalities; there were 18 fatalities involving acetaminophen, 9 as a single agent. There were 7 cases of carbon monoxide fatalities, an increase from previous years [1, 2, 4, 5].

In 2018, there were 11 pediatric (age 0–18 years) deaths due to a known toxicologic exposure (13.3%). The age range was 5 months to 18 years. Seven were single agent exposures and 4 involved multiple agents. Two polysubstance cases involved opioids in teenagers; there were no single agent opioid pediatric deaths. There were three deaths due to carbon monoxide exposure, and one death due to acute liver failure in a 5-month-old after an acetaminophen exposure. There was a report of a death secondary to non-synthetic cannabinoid exposure in a 16-year-old who developed hypotension, bradycardia,

Table 30 Toxidromes

	N (%)[a]
Sedative-hypnotic	761 (10.8)
Anticholinergic	464 (6.6)
Sympathomimetic	330 (4.7)
Opioid	268 (3.8)
Serotonin syndrome	192 (2.7)
Sympatholytic	48 (0.7)
Alcoholic ketoacidosis	46 (0.7)
NMS[b]	12 (0.2)
Cholinergic	11 (0.2)
Overlap syndromes (MCS, chronic fatigue, etc.)	11 (0.2)
Washout syndrome	8 (0.1)
Miscellaneous[c]	5 (0.1)
Total	2156 (30.8)

[a] Percentage equals number cases reporting specific toxidrome relative to total number of Registry cases in 2018 ($N = 7043$)

[b] NMS: neuroleptic malignant syndrome

[c] Includes anticonvulsant hypersensitivity, fume fever

Table 31 Major vital sign abnormalities

	N (%)[a]
Tachycardia (HR > 140)	835 (11.9)
Hypotension (systolic BP < 80 mmHg)	483 (6.9)
Bradycardia (HR < 50)	298 (4.2)
Hypertension (systolic BP > 200 mmHg and/or diastolic BP > 120 mmHg)	172 (2.4)
Bradypnea (RR < 10)	152 (2.2)
Hyperthermia (temp > 105 °F)	34 (0.5)
Total	1974 (28.1)[b]

HR heart rate, *BP* blood pressure, *RR* respiratory rate

[a] Percentage equals the number of cases relative to the total number of Registry cases in 2018 ($N = 7043$).

[b] Total reflects cases reporting at least one major vital sign abnormality. Cases may be associated with more than one major vital sign abnormality.

Table 32 Clinical signs and symptoms-neurological

	N (%)[a]
Coma/CNS depression	2087 (29.6)
Agitation	1036 (14.7)
Delirium/toxic psychosis	738 (10.5)
Hyperflexia/myoclonus/clonus/tremor	426 (6.0)
Seizures	420 (6.0)
Hallucinations	244 (3.5)
Weakness/paralysis	79 (1.1)
EPS/dystonia/rigidity	76 (1.1)
Numbness/paresthesia	56 (0.8)
Peripheral neuropathy (objective)	20 (0.3)
Total	3783(53.7)[b]

[a] Percentage based on the total number of Registry cases in 2018 ($N = 7043$)

[b] Total reflects cases reporting at least one neurologic symptom ($N = 3783$). Cases may have reported multiple neurological clinical effects

Table 33 Clinical signs–cardiovascular and pulmonary

	N (%)[a]
Cardiovascular	
Prolonged QTc (≥ 500 ms)	358 (5.1)
Prolonged QRS (≥ 120 ms)	108 (1.5)
Myocardial injury or infarction	97 (1.4)
Ventricular dysrhythmia	54 (0.8)
AV Block (> 1st degree)	25 (0.4)
Total	642 (9.1)[b]
Pulmonary	
Respiratory depression	681 (8.8)
Aspiration pneumonitis	103 (1.5)
Acute lung injury/ARDS[c]	73 (1.0)
Asthma/reactive airway disease	55 (0.8)
Total	849 (12.1)[b]

[a] Percentage equals number cases reporting signs of symptoms relative to total number of Registry cases in 2018 (*N* = 7043)

[b] Total reflects cases reporting at least one cardiovascular or pulmonary symptom. Cases may be associated with more than one symptom

[c] ARDS: acute respiratory distress syndrome

Table 34 Clinical signs–other organ systems

	N (%)[a]
Metabolic	
Elevated anion gap (> 20)	286 (4.1)
Metabolic acidosis (pH < 7.2)	276 (3.9)
Hypoglycemia (glucose < 50 mg/dL)	122 (1.7)
Elevated osmole gap (> 20)	28 (0.4)
Total	535 (7.6)[b]
Renal/musculoskeletal	
Acute kidney injury (creatinine > 2.0 mg/dL)	285 (4.0)
Rhabdomyolysis (CPK > 1000 IU/L)	263 (3.7)
Total	478 (6.8)[b]
Hematological	
Coagulopathy (PT > 15 s)	139 (2.0)
Leukocytosis (WBC > 20 K/μL)	82 (1.2)
Thrombocytopenia (platelets < 100 K/μL)	80 (1.1)
Hemolysis (Hgb < 10 g/dL)	47 (0.7)
Methemoglobinemia (MetHgb ≥ 2%)	23 (0.3)
Pancytopenia	7 (0.1)
Total	310 (4.4)[b]
Gastrointestinal/hepatic	
Hepatotoxicity (AST ≥ 1000 IU/L)	220 (3.1)
Gastrointestinal bleeding	40 (0.6)
Pancreatitis	29 (0.4)
Corrosive injury	24 (0.3)
Intestinal ischemia	4 (0.1)
Total	294 (4.2)[b]
Dermatological	
Rash	100 (1.4)
Blister/Bullae	75 (1.1)
Angioedema	31 (0.4)
Necrosis	20 (0.3)
Total	193 (2.7)[b]

AST aspartate aminotransferase, *PT* prothrombin time, *WBC* white blood cells, *Hgb* hemoglobin, *CPK* creatine phosphokinase

[a] Percentage equals the number of cases reporting specific clinical signs compared to the total number of Registry cases in 2018 (*N* = 7043)

[b] Total reflects cases reporting at least one sign in the category. Cases may be associated with more than one symptom

bradypnea, asthma/ARDS symptoms, and CNS depression as well as metabolic acidosis and leukocytosis. He was treated with naloxone, albuterol, steroids, benzodiazepines, and neuromuscular blockers.

There were 62 fatality cases in which life support was withdrawn, representing 0.9% of Registry cases and nearly doubling from 2017 [1]. It was unknown whether life support was withdrawn in an additional 11 cases. Brain death was declared in 32 cases; brain death confirmation status was unknown in an additional 14 cases.

Adverse Drug Reactions

Table 37 presents the common drugs associated with adverse drug reactions reported to the Registry in 2018. Lithium was again the most common drug reported (5.5%), similar to previous years [1–5]. Digoxin (4.8%) and valproic acid (4.8%) were the second most common agents. Bupropion was no longer amongst the most common agents this year, and tramadol emerged as one of the top 10 agents (3.6%).

Treatment

Antidotal Therapy Administered

Table 38 describes the 2331 antidotes reported to the Registry in 2018. Similar to previous years [1], N-acetylcysteine (40.0%), followed by naloxone/nalmefene (18.9%), and sodium bicarbonate (11.1%) were the most commonly reported antidotes.

Antivenom Therapy Administered

Table 39 presents data on antivenom therapies reported to the Registry. Crotalidae polyvalent immune fab (ovine) made up the majority (94.2%) of antivenom therapy administered. Other snake antivenoms and scorpion antivenom were also reported to the Registry in 2018.

Table 35 2018 Fatalities reported in ToxIC Registry with known toxicological exposure[a]: Single Agent

Age/ gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
20M	Abrus precatorious	TC, CNS, SZ, GIB, WBC, RFX, OTH1	Yes	No	None listed
41F	Acetaminophen	CNS, MA, HPT	Yes	Unknown	NAC, IV fluids
5mF	Acetaminophen	None listed	No	No	None listed
21F	Acetaminophen	CNS, HGY, MA, AG, HPT, GIB, AKI	Yes	No	Folate, NAC, thiamine, vitamin K, benzodiazepines, IV fluids
59M	Acetaminophen	HT, TC, ALI, CNS, HGY, MA, HPT, CPT, AKI, RBM	No	No	NAC, vasopressors, hemodialysis, continuous renal replacement, intubation, IV fluids
57F	Acetaminophen	CNS, DLM, HGY, MA, AG, HPT, WBC	Yes	Unknown	NAC, glucose > 5%, intubation
37M	Acetaminophen	HT, CNS, HGY, MA, AG, HPT, PNC, CPT, PLT, AKI	Yes	No	Fomepizole, NAC, vasopressors, glucose > 5%, opioids, intubation IV fluids
54F	Acetaminophen	HT, QTC, RD, CNS, MA, AG, HPT, AKI	Yes	No	NAC, physostigmine, vasopressors, intubation, IV fluids
42F	Acetaminophen	HT, CNS, HGY, MA, AG, HPT, AKI, OTH2	Yes	No	Factor replacement, NAC, vitamin K, vasopressors, glucose > 5%, activated charcoal
32F	Acetaminophen	HT, HTN, BP, VD, AGT, CNS, MA, AG, HPT, CPT	No	No	NAC, vasopressors, antiarrhythmics, antipsychotics, steroids, activated charcoal, hemodialysis, intubation, IV fluids, transfusion
61M	Alprazolam	HT, TC, QTC, MI, RD, CNS, MA, AKI	Unknown	Unknown	None listed
50M	Aspirin	ALI, AG	Yes	Unknown	$NaHCO_3$, urinary alkalinization, IV fluids
16M	Canabinoid nonsynthetic	HT, BC, BP, RAD, CNS, MA, WBC	Yes	Yes	Naloxone/nalmefene, albuterol, benzodiazepines, neuromuscular blockers, steroids, CPR, intubation, IV fluids
44M	Carbamazepine	CNS	Yes	Yes	None listed
35F	Carbon monoxide	None listed	No	No	None listed
23M	Carbon monoxide	CNS	No	No	HBO
23F	Carbon monoxide	HT, TC, ALI, CNS, MA, AG	Yes	Yes	Hydroxocobalamin, $NaHCO_3$, thiosulfate, vasopressors, antiarrhythmics, neuromuscular blockers, steroids
9M	Carbon monoxide	HT, ALI, RD, CNS, MA, AG,	No	No	Hydroxocobalamin, thiosulfate, vasopressors, CPR, intubation, IV fluids
66F	Carbon monoxide	HT, BC, ALI, RD, CNS,	No	No	None listed
10M	Carbon monoxide	HT, RD, CNS, AG	Yes	Yes	Intubation, IV fluids
56F	Clonidine	BC, CNS	Yes	Yes	Vasopressors, intubation, IV fluids
46M	Cocaine	SZ, VD	Yes	Yes	None listed
18 mM	Dextroamphetamine	TC, AGT	No	No	Benzodiazepines, IV fluids
48F	Diltiazem	HT, BC, ALI, MA, AG	No	No	Calcium, HIE, $NaHCO_3$, vasopressors, benzodiazepines, glucose > 5%, neuromuscular blockers, activated charcoal, continuous renal replacement therapy, ECMO, intubation, IV fluids
31M	Diltiazem	HT, BC, AVB, ALI, AP, HPT, CPT, BL	Yes	Unknown	Calcium, HIE, vasopressors, CPR, ECMO, intubation, IV fluids
13F	Diphenhydramine	HT, TC, QRS, RD, CNS, SZ	Yes	Yes	$NaHCO_3$, vasopressors, anticonvulsants, benzodiazepines, neuromuscular blockers, CPR, intubation, IV fluids
59F	Ethanol	HT, CNS, MA, AG, GIB, CPT, PLT, WBC	No	Unknown	Fomepizole, octreotide, $NaHCO_3$, thiamine, vitamin K, vasopressors, CPR, intubation, IV fluids, transfusion
29F	Ethylene glycol	AG, AKI	Yes	No	Fomepizole, hemodialysis
34F	Fentanyl	HT, RD, CNS, AKI	Yes	Yes	Naloxone, vasopressors, intubation, IV fluids
35M	Fentanyl	HT, BC, BP, VD, MI, RD, CNS, SZ, MA, AG, HYS	Yes	Yes	NAC, naloxone, $NaHCO_3$, vasopressors, antiarrhythmics, antipsychotics, benzodiazepines, neuromuscular blockade, opioids, CPR, intubation, IV fluids
77F	Flecainide	HT, BC, VD, QRS, QTC, AVB, MI, ALI, AP, CNS, MA, HPT, AKI	Yes	No	HIE, $NaHCO_3$, vasopressors, continuous renal replacement therapy, CPR, intubation
38M	Heroin	CNS	No	No	Naloxone
26F	Heroin	HT, QTC, RD, CNS	Yes	Yes	Naloxone, CPR, intbuation
45F	Insulin	TC, QTC, RD, CNS	Yes	Unknown	Naloxone, glucose > 5%, intubation, IV fluids

Table 35 (continued)

Age/ gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
38F	Lidocaine	HT, BC, AGT	No	No	HIE, vasopressors, CPR, IV fluids
57M	Metaxalone	HT, QTC, RD, CNS, MA	No	No	Vasopressors, continuous renal replacement therapy, intubation
48M	Methadone	CNS	Yes	Yes	Naloxone, vasopressors, intubation, IV fluids
48F	Methadone	HT, CNS	Yes	Yes	Vasopressors, antiarrhythmics, intubation, IV fluids
86 M	Methotrexate	HYT, GIB, HYS, CPT, PLT, PCT	Yes	No	None listed
29F	Oxycodone	HT, ALI, CNS, MA, AKI, RBM	No	No	Naloxone, vasopressors, intubation
43M	Phentolamine	HT, TC, CNS, AKI	Yes	No	Vasopressors, intubation,
19F	Propranolol	HTN, TC, BC, VD, AVB, ALI, RD, CNS, SZ, MA	No	No	Calcium, glucagon, HIE, $NaHCO_3$, vasopressors, anticonvulsants, benzodiazepines, glucose > 5%, CPR, intubation, IV fluids
45M	Quinine	VD, CNS, AKI, RBM	Yes	Yes	Naloxone, intubation
19M	Sodium hypochlorite <6%	HT, CRV	No	No	None listed
10M	Unknown agent	HT, RD, CNS	Unknown	Unknown	Naloxone prevention kit, vasopressors, CPR, intubation
87F	Verapamil	HT, BC, QTC, AVB, ALI, AKI	Yes	Unknown	HIE, vasopressors, glucose > 5%, IV fluids
40M	Water	RD, CNS, SZ	Yes	Yes	Folate, thiamine, anticonvulsants, benzodiazepines, intubation, mannitol
62M	None listed	AG, HPT, PNC	No	No	NAC, vasopressors, continuous renal replacement therapy, intubation, IV fluids
70M	None listed	None listed	Unknown	Unknown	None listed

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals Yes with known agent(s)

[b] Age in years unless otherwise stated. wk: weeks, m: months

[c] AG: anion gap, AGT: agitation, AKI: Acute kidney injury, ALI: acute lung injury/ARDS, AP: aspiration pneumonia, AVB: AV block, BC: bradycardia, BL: blisters/bullae, BP: bradypnea, CNS: coma/ CNS depression, CPT: coagulopathy, CRV: corrosive injury, DLM: delirium, GIB: GI bleeding, HGY: hypoglycemia, HPT: hepatoxicity, HT: hypotension, HTN: hypertension, HYS: hemolysis, HYT: hyperthermia, MA: metabolic acidosis, MI: myocardial injury/ischemia, OTH1: choreoathetoid movement, OTH2: hypothermia, PCT: pancytopenia, PLT: thrombocytopenia, PNC: pancreatitis, QTC: QTc prolongation, RAD: asthma/reactive airway disease, RBM: rhabdomyolysis, RD: respiratory depression, RFX: hyperreflexia/tremor, SZ: seizures, TC: tachycardia, VD: ventricular dysrhythmia, WBC: leukocytosis

[d] Pharmcological and non-pharmacological support as reported by Medical Toxicologist; BAL: Dimercaprol, CPR: Cardiopulmonary resuscitation, ECMO: Extra-corporeal membrane oxygenation, HBO: hyperbaric oxygenation, HIE: high dose insulin euglycemic therapy, NAC: n-Acetyl cysteine, $NaHCO_3$: Sodium bicarbonate

Table 36 2018 Fatalities reported in ToxIC Registry with known toxicological exposure[a]: Multiple Agents

Age/ gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
36F	Acetaminophen, pregabalin	HT, VD, QRS, RD, CNS, MA, AG	Yes	Yes	NAC, vasopressors, glucose > 5%, CPR, intubation, IV fluids
43M	Acetaminophen, diphenhydramine, ranitidine, citalopram	HT, MI, ALI, AP, CNS, HGY, MA, HPT, CPT, PLT, AKI	Yes	Yes	Folate, NAC, octreotide, bicarbonate, thiamine, vasopressors, continuous renal replacement therapy, intubation, IV fluids, phenobarbital
52M	Acetaminophen, codeine	HT, AP, CNS, HGY, MA, HPT, AKI	Unknown	Unknown	Calcium, fomepizole, NAC, $NaHCO_3$, vasopressors
53F	Acetaminophen, metformin	HT, RD, CNS, MA, HPT, CPT, PLT	No	No	NAC, vitamin K, vasopressors, continuous renal replacement therapy, CPR, intubation, IV fluids
57F	Acetaminophen, hydrocodone, diazepam	HT, ALI, RD, CNS, HGY, MA, HPT, INT, CPT, AKI, RBM, BL	Yes	No	NAC, vasopressors, glucose 5%, continuous renal replacement therapy, intubation, IV fluids
63F	Acetaminophen, ibuprofen	ALI, RD, CNS, MA, AG, HPT, HYS, CPT, AKI	Yes	Yes	NAC, vitamin K, vasopressors, glucose > 5%, continuous renal replacement therapy, urinary alkalinization, intubation, IV fluids, transfusion
74F	Acetaminophen, metformin	HT, QTC, DLM, MA, AG, OG, HPT	Unknown	Unknown	NAC, vasopressors, hemodialysis, intubation
62F	Amitriptyline, caustic unspecified	TC, VD, QRS, QTC, ALI, AP, CNS, SZ, MA, AG	No	No	$NaHCO_3$, vasopressors, hemodialysis
55F	Amlodipine, atenolol	HT, CNS, MA	No	No	Calcium, glucagon, HIE, methylene blue $NaHCO_3$, vasopressors, continuous renal replacement therapy, intubation, IV fluids
32M	Anticonvulsant unspecified, olanzapine, lamotrigine, bupropion	None listed	No	No	None listed
12F	CO, smoke, cyanide	HT, TC, ALI, CNS, MA, AG, CPT, WBC, AKI	No	No	Hydroxocobalamin, $NaHCO_3$, vasopressors, continuous renal replacement therapy, intubation, IV fluids
79F	Carvedilol, amiodarone, ibuprofen, apixaban	HT, BC, VD, MI, RD, CNS, GIB, CPT, AKI	No	No	Factor replacement, glucagon, HIE, vasopressors, intubation, IV fluids, transfusion
71F	Cefepime, metronidazole	CNS	No	No	None listed
50M	Cocaine, fentanyl, cannabinoid non-synthetic	HT, QTC, MI, ALI, RD, CNS, MA, AG, AKI, RBM	Yes	Yes	None listed
63M	Cocaine, amphetamine, methamphetamine, fentanyl, acetyl fentanyl	HT, TC, VD, MI, ALI, CNS, MA, AG, OG, HPT, AKI, RBM	Unknown	Unknown	Fomepizole, vasopressors, continuous renal replacement therapy, intubation, IV fluids
14M	Dextromethorphan, oxycodone	HT, BC, QRS, QTC, RD, CNS, MA	Yes	Yes	NAC, naloxone, vasopressors, intubation, IV fluids
61F	Diltiazem, fluoxetine	HTN, HT, TC, BC, CNS, SZ, MA	No	No	Atropine, calcium, HIE, methylene blue, $NaHCO_3$, vasopressors, opioids, continuous renal replacement therapy, intubation
27M	Doxylamine, loperamide	HT, TC, BC, VD, QRS, QTC, AVB, RD	Yes	Unknown	$NaHCO_3$, vasopressors, antiarrhythmics, CPR, ECMO, intubation, IV fluids, transvenous pacer, hypertonic saline
34F	Ethanol, acetaminophen	CNS, HGY, MA, HPT, HYS, CPT	Yes	Unknown	Fomepizole NAC, $NaHCO_3$, thiamine, vasopressors, opioids, intubation, IV fluids, transfusion
68F	Ethylene glycol, unknown agent	HT, AP, RD, CNS, MA, AG, AKI	Yes	No	Fomepizole, pyridoxine, vasopressors, steroids, continuous renal replacement therapy, ECMO, intubation
29F	Fentanyl, marijuana	QTC, MI, ALI, CNS, SZ, MA, AG	Yes	Yes	

Table 36 (continued)

Age/ gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
					Fomepizole, vasopressors, anticonvulsants, benzodiazepines, neuromuscular blockers, steroids, CPR, intubation, IV fluids, therapeutic hypothermia
51F	Fentanyl, acetaminophen, valproic acid	HT, BP, RD, CNS, HPT	Yes	Unknown	Carnitine, NAC, naloxone, intubation
57M	Fentanyl, benzodiazepine unspecified	HT, BC, QTC, MI, RD, CNS, MA	Yes	Yes	Naloxone, $NaHCO_3$, vasopressors, CPR, intubation, IV fluids, therapeutic hypothermia, $MgSO_4$
25M	Heroin, fentanyl, gabapentin	HT, VD, CNS	Yes	Yes	Naloxone prevention kit, benzodiazepines, opioids, intubation, IV fluids
32M	Heroin, diphenhydramine	BP, MI, MI, ALI, RD, CNS	Yes	Yes	Naloxone, vasopressors, intubation, IV fluids
16F	Iron, ibuprofen, apixaban	HT, ALI, CNS, MA, AG, HPT, CPT, PLT, WBC	Yes	Yes	Vitamin K, deferoxamine, vasopressors, benzodiazepines, continuous renal replacement therapy, intubation, IV fluids, transfusion
18M	Loperamide, fentanyl, dextromethorphan, propylhexedrine	HT, TC, AP, RD, CNS, RFX, MA, AG, AKI	Unknown	Unknown	Naloxone, vasopressors, anticonvulsants, benzodiazepines, neuromuscular blockers, intubation, IV fluids
78M	Lorazepam, gabapentin	None listed	Unknown	Unknown	None listed
68M	Metformin, glyburide	RD, CNS, MA, HPT, PCT	Yes	Yes	Vitamin K, vasopressors, hemodialysis, intubation, IV fluids
81F	Metoprolol, diltiazem	HTN	No	No	Glucagon, vasopressors
52M	Morphine, oxycodone, lorazepam	Ischemic CVA	Unknown	Unknown	None listed
58M	Morphine, oxycodone	HT, BC, VD, QRS, QTC, RD, CNS, RFX, CPT, AKI	Yes	Unknown	Calcium, $NaHCO_3$, vasopressors, antiarrhythmics, anticonvulsants, benzodiazepines, neuromuscular blockers, intubation, IV fluids, therapeutic hypothermia
40F	Oxycodone, alprazolam, promethazine	HT, TC, MI, ALI, CNS, DLM, SZ, MA, AG, HPT, GIB, INT, PLT, AKI, RBM	Unknown	Unknown	NAC, vasopressors, antiarrhythmics, anticonvulsants, benzodiazepines, neuromuscular blockers, hemodialysis, CPR, intubation, IV fluids, therapeutic hypothermia, transfusion
43F	Venlafaxine, amlodipine, risperidone	HT, BC, CNS, AKI	No	No	Atropine, calcium, HIE, methylene blue, vasopressors, neuromuscular blockers, activated charcoal, intubation, IV fluids

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals Yes with known agent(s)

[b] Age in years unless otherwise stated. wk: weeks, m: months

[c] AG: anion gap, AGT: agitation, AKI: Acute kidney injury, ALI: acute lung injury/ARDS, AP: aspiration pneumonia, AVB: AV block, BC: bradycardia, BL: blisters/bullae, BP: bradypnea, CNS: coma/CNS depression, CPT: coagulopathy, CRV: corrosive injury, DLM: delirium, EPS: dystonia, GIB: GI bleeding, HCN: hallucinations, HGY: hypoglycemia, HPT: hepatoxicity, HT: hypotension, HTN: hypertension, HYS: hemolysis, HYT: hyperthermia, INT: intestinal ischemia, MA: metabolic acidosis, MET: methemoglobinemia, NP: neuropathy, OG: osmole gap, OTH1: Rash, OTH2: Skin blisters, necrosis, PCT: pancytopenia, PLT: thrombocytopenia, PNC: pancreatitis, PST: paresthesia, QRS: QRS prolongation, QTc: QTc prolongation, RAD: asthma/reactive airway disease, RBM: rhabdomyolysis, RD: respiratory depression, RFX: hyperreflexia/tremor, SZ: seizures, TC: tachycardia, VD: ventricular dysrhythmia, WBC: leukocytosis, WKN: weakness/paralysis

[d] Pharmcological and Non-pharmacological support as reported by Medical Toxicologist; BAL: Dimercaprol, CPR: Cardiopulmonary resuscitation, ECMO: Extra-corporeal membrane oxygenation, NAC: n-Acetyl cysteine, $NaHCO_3$: Sodium bicarbonate

Table 37 Most common drugs associated with ADRs

	N (%)[a]
Lithium	9 (5.5)
Digoxin	8 (4.8)
Valproic acid	8 (4.8)
Dapsone	7 (4.2)
Haloperidol	7 (4.2)
Sertraline	7 (4.2)
Insulin	6 (3.6)
Metformin	6 (3.6)
Tramadol	6 (3.6)

[a] Percentage based on the total number of Registry cases reporting an ADR in 2018 (*N* = 165) *ADR* adverse drug reaction

Pharmaceutical Supportive Care

Table 40 describes the 2062 pharmaceutical supportive care treatments reported in 2018. Benzodiazepines were again the most commonly reported agents (52.9%) [1] followed by vasopressors (11.0%) and opioids (10.9%). Year 2018 is the first year since 2014 that opioids fell below the second most commonly reported pharmaceutical supportive care treatment [1–5].

Non-pharmaceutical Supportive Care

Table 41 presents non-pharmaceutical supportive care treatments reported to the Registry in 2018. The top two agents, IV fluid resuscitation (70.2%) and intubation/ventilatory management (25.5%), remain unchanged from last year and represent the large majority of agents in this category [1].

Chelation Therapy Administered

Table 42 presents data on chelation therapy administered. There were 19 cases involving chelation reported in 2018, with 6 cases involving more than 1 chelator. One case reported three different chelators. DMSA was the most commonly reported (38.5%), followed by EDTA (26.9%).

Decontamination Interventions Administered

Table 43 describes the 212 decontamination interventions administered. Activated charcoal again represented the significant majority (78.8%) in this class [1].

Enhanced Elimination Interventions Administered

Table 44 presents the enhanced elimination interventions reported. This year, hemodialysis for toxin removal (24.7%) and for other causes (24.7%), followed by continuous renal replacement therapy (24.2%) topped the reported interventions in this class.

Table 38 Antidotal therapy

	N (%)[a]
N-acetylcysteine	768 (32.9)
Naloxone/nalmefene	441 (18.9)
Sodium bicarbonate	259 (11.1)
Thiamine	157 (6.7)
Folate	95 (4.1)
Physostigmine	84 (3.6)
Fomepizole	79 (3.4)
Glucagon	66 (2.8)
Calcium	50 (2.1)
Atropine	42 (1.8)
Octreotide	40 (1.7)
Insulin-euglycemic therapy	34 (1.5)
Vitamin K	34 (1.5)
Carnitine	33 (1.4)
Flumazenil	33 (1.4)
Methylene blue	28 (1.2)
Cyproheptadine	27 (1.2)
Pyridoxine	15 (0.6)
Fab for digoxin	10 (0.4)
Hydroxocobalamin	8 (0.3)
2-PAM	6 (0.3)
Botulinum antitoxin	4 (0.2)
Dantrolene	4 (0.2)
Ethanol	4 (0.2)
Bromocriptine	3 (0.1)
Thiosulfate	3 (0.1)
Anticoagulation reversal	1 (<0.1)
Silimarin	1 (<0.1)
Total	2331 (100)

[a] Percentages are out of the total number of antidotes administered (2331); 1920 (27.3%) cases received at least one antidote. Cases may have involved the use of multiple antidotes.

Table 39 Antivenom therapy

	N (%)[a]
Crotalidae polyvalent immune fab (ovine)	162 (94.2)
Other snake antivenom	7 (4.1)
Scorpion antivenom	3 (1.7)
Total	172 (100)

[a] Percentages are out of the total number of antivenom treatments administered (*N* = 172).

Table 40 Supportive care-pharmacologic

	N (%)[a]
Benzodiazepines	1446 (52.9)
Vasopressors	302 (11.0)
Opioids	298 (10.9)
Antipsychotics	184 (6.7)
Anticonvulsants	114 (4.2)
Glucose > 5%	102 (3.7)
Neuromuscular blockers	99 (3.6)
Antihypertensives	58 (2.1)
Steroids	47 (1.7)
Albuterol and other bronchodilators	38 (1.4)
Antiarrhythmics	22 (0.8)
Beta-blockers	22 (0.8)
Vasodilators	2 (0.1)
Total	2734 (100)

[a] Percentage based on the total number of interventions (3574). A total of 2062 registry cases (29.3%) received at least one pharmacologic intervention. Cases may have involved the use of multiple interventions

Discussion

This report describes the 9th year of data collected for the Toxicology Investigators' Consortium Registry. The small reduction in reported cases this year represents a consistent trend over time. This issue is multifactorial, but a primary reason is persistent efforts for quality control in the Registry; poorly performing sites are frequently reviewed and removed.

Table 41 Supportive care–nonpharmacological

	N (%)[a]
IV fluid resuscitation	2249 (70.2)
Intubation/ventilatory management	815 (25.5)
CPR	49 (1.5)
Transfusion	30 (0.9)
Hyperbaric oxygen	14 (0.4)
Cardioversion	12 (0.4)
ECMO	10 (0.3)
Pacemaker	9 (0.3)
Therapeutic hypothermia	9 (0.3)
Organ transplantation	3 (0.1)
Aortic balloon pump	1 (0.03)
Cardiopulmonary bypass	1 (0.03)
Total	3202 (100)

[a] Percentages are out of the total number of treatments administered (3202); 2526 registry cases (35.9%) received at least one form of nonpharmacological treatment. Cases may have involved the use of multiple forms of treatment

CPR cardiopulmonary resuscitation, *ECMO* extracorporeal membrane oxygenation

Table 42 Chelation therapy

	N (%)[a]
DMSA	10 (38.5)
EDTA	7 (26.9)
Deferoxamine	6 (23.1)
Dimercaprol	3 (11.5)
Total	26 (100)

[a] Percentages are out of the total number of chelation treatments administered (26); 19 registry cases (0.2%) received at least one form of chelation treatment

DMSA dimercaptosuccinic acid, *EDTA* ethylenediamine-tetraacetic acid

Although the Registry is not strictly population based but it represents a wide geographic distribution of cases evaluated in person by medical toxicologists. These data can be used in conjunction with data from other registries including the National Poison Data System to provide a more detailed picture of poisoning trends, novel exposures, and their public health implications.

Trends in novel exposures were not described in this report but are being collected and analyzed to be reported separately.

Overall, this annual report finds trends in agent classes, agents, demographics, types of encounters, clinical signs and symptoms, and treatments to be largely unchanged from previous years. Notable findings or trends in the Registry are discussed below.

Although the overall reported opioid exposures reported to the Registry has leveled off compared to last year, the relative impact of individual agents appears to be evolving, consistent with national trends [9]. Relative heroin and fentanyl exposures increased in the Registry in 2018, whereas there was a relative reduction in oxycodone and tramadol cases reported.

Additionally, in 2018, there was an increase in psychoactive substances reported; notably, this increase was reflective of an increase in non-synthetic cannabinoids including marijuana. This national trend is consistent with trends in the pediatric population which have shown an increase in marijuana exposures, particularly after legalization [10, 11].

Table 43 Supportive care-decontamination

	N (%)[a]
Activated charcoal	167 (78.8)
Whole bowel irrigation	30 (14.2)
Irrigation	12 (5.7)
Gastric lavage	3 (1.4)
Total	212 (100)

[a] Percentage based on the total number of interventions (212); 208 registry cases (3.0%) received at least one decontamination intervention. Cases may have involved the use of multiple interventions

Table 44 Enhanced elimination

	N (%)[a]
Urinary alkalinization	64 (26.4)
Hemodialysis (toxin removal)	60 (24.8)
Continuous renal replacement therapy	60 (24.8)
Hemodialysis (other indication)	45 (18.6)
Multiple-dose activation charcoal	11 (4.5)
Exchange Transfusion	2 (0.8)
Total	219 (100)

[a] Percentages are out of the total number of treatments administered (219); 191 registry cases (2.7%) received at least one form of enhanced elimination

Older Adults

Older adults represented 4.7% of registry cases. Interestingly, the top agent class reported for older adults was the cardiovascular class, which differs from the overall registry as well as from data on self-harm cases in this age category [12]. Additionally, the relative impact of cardiovascular agents increased with age, with 22.9% of agents reported in adults > 85 years of age belonging to the cardiovascular class. A possible explanation for this divergence is the nature of cases reported to the Registry. Registry cases require bedside medical toxicology evaluation, and thus may skew towards sicker cases when compared to more population-based registries such as Poison Center data. Cardiovascular agents have significant potential to cause morbidity and mortality, particularly in the extremes of age, perhaps resulting in the increased numbers seen in older adults in the Registry. Other publications have found similar trends [1, 13]. In the pediatric analysis of the 2017 Registry annual report, cardiovascular drugs were also found to be the most common agent reported in children aged 5 or younger [1].

When intent of older adult exposures was analyzed, differing trends from the larger Registry were found. Consistent with the larger Registry, intentional pharmaceutical exposures were the most common reason for encounter. Among these, self-harm was the most frequent intent (41.9%). The second most frequent detailed reason was therapeutic use (34.9%), which differed from the larger Registry where only 7.9% of cases resulted from therapeutic use. The low therapeutic index and potential for drug interactions among cardiovascular drugs may have contributed to the high number of cases in this age group. Indeed, within intentional pharmaceutical exposures in older adults, a large number (21.4%) of cardiovascular agent exposures were the result of therapeutic use.

Table 45 Seizures after bupropion ingestion

	N (%)
All Exposures	
Bupropion	79(18.8)
Other agent	341 (81.2)
Total	420 (100)
Bupropion Ingestions	
Seizure	79 (32.2)
No seizure	166 (67.8)
Total	245 (100)

Seizures and Bupropion

Given bupropion is a commonly used antidepressant with abuse potential and is associated with seizures, registry data was evaluated to determine the seizure rate in this study population. Table 45 reports that in 2018, there was a total of 420 exposures that were complicated by seizure activity, with 79 (19%) of these being secondary to bupropion ingestions. Looking at bupropion ingestions specifically, there were 245 total reported cases. Seizure activity was reported in 79 (32%) of these cases. The amount of bupropion ingested was not reported in all cases, making a dose-response relationship

Table 46 Treatment of withdrawal

	N (%)[a]
Opioid withdrawal	
Buprenorphine	31 (43.7)
Clonidine	21 (29.6)
Methadone	14 (19.7)
Naloxone OD kit	3 (4.2)
Clonazepam	1 (1.4)
Ondansetron	1 (1.4)
Total	71 (100)
Ethanol withdrawal	
Naltrexone	3 (42.9)
Buprenorphine	3 (42.9)
Clonidine	1 (14.3)
Total	7 (100)
Sedative-hypnotic withdrawal	
Phenobarbital	1 (33.3)
Methadone	1 (33.3)
Clonidine	1 (33.3)
Total	3 (100)

[a] Percentage based on the total number of treatments administered (opioid $N = 71$, ethanol $N = 7$, sedative-hypnotic $N = 3$). Fifty-nine (0.8%) registry opioid withdrawal cases, 6 (0.1%) registry ethanol withdrawal cases, and 3 (0.0%) registry sedative-hypnotic cases received at least one type of withdrawal treatment

Table 47 ToxIC 2018 centers of Medicare and Medicaid services-approved medical toxicology quality measures

Title	Numerator	Denominator	Exclusions
Screening for risk of opioid misuse/overuse	Patients who were screened for the potential risk of opioid misuse/overuse with a standardized tool (e.g., DAST, ASSIST) or assessed for the presence of any specific risk factors	Patients aged 12 years or older	None
Pregnancy test in women who receive a toxicologic consult	Patients who receive a pregnancy test prior to emergency department discharge or within 24 h of hospital admission	Women of childbearing age (12-60 years) who receive a toxicologic consult	Women who have had a hysterectomy or oophorectomy; minor dermal caustic exposure; Woman who are post-menopausal
EKG assessment in acute overdoses	Patients who have an EKG QRS and QTC duration assessment within 60 min of arrival to the emergency department	All intentional pharmaceutical overdoses of any age	Patients who present to the emergency department in cardiac arrest; exploratory pediatric ingestions with non-cardiotoxic ingestions
Appropriate treatment for acute acetaminophen ingestion	Patients for whom n-acetylcysteine (NAC) was received within 2 h of presentation and NAC treatment was discontinued appropriately	Patients of any age with acetaminophen poisoning receiving IV NAC	Patients with an acute single acetaminophen ingestion occurring less than 4 h or more than 24 h prior to presentation; Patients taking therapeutic doses of acetaminophen; Patients with hepatic failure as defined by encephalopathy and INR > 1.5
Assessment of suspected ethylene glycol or methanol exposures	Patients for whom the appropriate laboratory testing was completed within 4 h of hospital presentation	Patients of any age with suspected exposure to ethylene glycol or methanol	Serum osmolality and quantitative ethylene glycol/methanol testing not available; unintentional accidental ingestions of ethylene glycol or methanol
Repeat assessment of salicylate concentrations in overdose patients	Patients who received a second plasma salicylate concentration within 4 h following the initial test	Patients of any age with suspected drug overdose with an initial plasma salicylate concentration > 15 mg/dL	Patients who died within 4 h of the initial test; Patients who did not experience a drug overdose; patients on hemodialysis within 4 h of initial test

unavailable. Additionally, these ingestions were not all single agent bupropion overdoses; therefore, other drugs may be responsible for the reported seizures.

Addiction Medicine and Substance Use Disorder Consultation

In 2018, the ToxIC Registry added additional data field questions to more specifically evaluate services performed by medical toxicologists in care of patients with addiction and substance use disorder. While there is clearly overlap in toxicology patients who may have been evaluated for both addiction and another toxicologic indication, a field was added to identify cases in which the primary reason for consultation was related to addiction. In 2018, 244 case entries were identified with addiction as a primary visit indication, of which 146 (60%) were male. The mean age of 38.6 years was the same for both males and females. The majority, 209 (86%) of these encounters were performed as consultation in the Emergency Department or inpatient setting, although 25 (10%) were performed by an admitting Medical Toxicologist.

Opioid agonist initiation using methadone or a buprenorphine product was the most commonly reported consult activity (47%), followed by pain management (14%); counseling/support was reported infrequently (5%). When opioid agonist initiation was reported, the dual product buprenorphine/naloxone was used in 99 (75%) followed by methadone in 20 (15%) and buprenorphine alone in 9 (4%) cases. Naltrexone was used for opioid antagonist initiation in only 4 encounters and was also used for alcohol use disorder in 8 encounters. Adjunct use of clonidine was reported in 17 (13%) cases in which initiation of an opioid agonist occurred. Specific drugs were reported for substance use disorder in 116 (47%) of cases. Heroin was reported most frequently in 72% of cases, 75% of which used the parenteral route. Oxycodone was the second most commonly reported drug (11%). Buprenorphine, fentanyl, methadone, and loperamide were also specifically reported as opioids of abuse. In addition to opioids, ethanol (17%) and stimulants (4%) were also reported.

In addition to the addiction cases, there were 183 cases identified in which treatment of withdrawal or misuse/abuse of substances was the primary indication for the encounter.

Sixty-eight of these cases were specifically identified and treated as withdrawal. Table 46 describes the treatments reported in these patients.

QCDR

On December 29, 2017 The Centers for Medicare and Medicaid Services (CMS) approved the ToxIC Registry as a Qualified Clinical Data Registry (QCDR). A QCDR is a registry recognized by CMS as a tool to collect data on quality metrics. Starting the 2018 calendar year, the ToxIC Qualified Clinical Data Registry (TQCDR) now serves as a platform to report on medical toxicology measures to CMS. Along with approving the QCDR, CMS also approved 6 medical toxicology quality measures (see Table 47). Therefore, ToxIC serves as the data collection tool and reporting mechanism for these quality measures. These toxicology-specific measures allow medical toxicologists to report on measures that matter most to their practices. These are the first measures specifically designed for and by medical toxicologists. In 2018, 44 medical toxicologists participated in the TQCDR.

Limitations

The ToxIC Registry is a unique prospective database of cases in which bedside consultation is performed by medical toxicologists, allowing an informed relationship between exposures and clinical outcomes. There are, however, some limitations within the Registry. One of these is a possible bias towards inclusion of more severe case presentations, since cases are only included if they undergo subspecialty bedside consultation. Cases for which a medical toxicology consultation was not requested are not reported and may represent a group with less severe illness. Therefore, the Registry likely represents a different population from other data sources such as Poison Control Centers. There may also be a disproportionate number of certain cases reported based on regional variations in drug use, abuse, and other toxic exposures. The ToxIC registry includes sites from multiple, diverse locations, but the entire country is not uniformly represented. Larger academic medical centers with greater amounts of medical toxicology faculty may be over-represented in the database.

Additionally, there may be a reporting bias towards more complicated or interesting cases at the level of individual sites. Although the express intent of the Registry, as defined in written agreements with all sites, is to obtain a consecutive sample of all cases at a given site, individual cases may be missed. Data regarding substances of exposure or species of envenomation relies heavily on patient self-report and may be misclassified. Willingness to disclose this information may be particularly true of illicit drug exposure. Lastly, the registry strives to continually improve the quality of data collected. While member sites are instructed to complete all applicable data fields, there are still a number of cases and data fields with incomplete information. This remains an issue for collection of race and ethnicity, for example. Efforts continue to support quality data collection and follow up on missing data where applicable.

Conclusions

The ToxIC Registry continues to be unique among databases in that it represents prospective data collected from cases evaluated at the bedside by medical toxicologists. Although this feature limits extrapolation to the population as a whole, it increases the potential for high quality data and for increased correlation between exposure cases and clinical findings. Continued quality improvement and surveillance efforts remain areas of focus for the Registry.

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Conflict of Interest None.

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