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The Toxicology Investigators Consortium Case Registry—the 2021 Annual Report

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Abstract

The Toxicology Investigators Consortium (ToxIC) Core Registry was established by the American College of Medical Toxicology in 2010. The Core Registry collects data from participating sites with the agreement that all bedside and telehealth medical toxicology consultations will be entered. This twelfth annual report summarizes the registry's 2021 data and activity with its additional 8552 cases. Cases were identified for inclusion in this report by a query of the ToxIC database for any case entered from January 1 to December 31, 2021. 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class, clinical signs and symptoms, treatments and antidotes administered, mortality, and whether life support was withdrawn. Gender distribution included 50.4% of cases in females, 48.2% of cases in males, and 1.4% of cases in transgender or gender non-conforming individuals. Non-opioid analgesics were the most commonly reported agent class (14.9%), followed by opioids (13.1%). Acetaminophen was the most common agent reported. Fentanyl was the most common opioid reported and was responsible for the greatest number of fatalities. There were 120 fatalities, comprising 1.4% of all cases. Major trends in demographics and exposure characteristics remained similar to past years' reports. Sub-analyses were conducted to describe new demographic characteristics, including marital status, housing status and military service, the continued COVID-19 pandemic and related toxicologic exposures, and novel substances of exposure.

Keywords Poisoning · Overdose · Surveillance · Epidemiology · Medical toxicology

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Introduction

In 2021, 8552 individual cases were entered into the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) Core Registry deriving

from 34 sites comprising 55 separate health care facilities. As of December 31, 2021, there were a total of 87,790 cases in the Core Registry.

The 2021 ToxIC initiatives included expansion of participating registry sites, initiation of new research initiatives, and continued support and expansion of existing research efforts. The registry welcomed the addition of five new sites and launched one new research partnership program entitled "Novel Opioid and Stimulant Exposures (NOSE)." Additionally, ToxIC supported and expanded efforts for two existing research partnerships initiated in 2020: the ToxIC Fentalog Project and the ToxIC FDA ACMT COVID-19 Pharmacovigilance Project (FACT).

ToxIC Novel Opioid and Stimulant Exposures (NOSE) Project

The ToxIC Novel Opioid and Stimulant Exposures (ToxIC NOSE) project began in 2021 with funding through the American Association of Addiction Psychiatry and in partnership with the Opioid Response Network (ORN). Through this collaboration, ToxIC enhanced the sentinel event detection instrument to better identify and characterize novel opioid and psychostimulant exposures. These data are used to generate quarterly reports highlighting novel exposures and interesting trends in novel opioid and stimulant exposures reported to the registry. Additionally, the project provides educational outreach for ACMT and ORN members on topics related to ToxIC NOSE reports in the form of webinars and tweetchats. The NOSE project has released quarterly online reports since beginning in January 2021 highlighting interesting cases and trends.

ToxIC Fentalog Project

This multicenter 5-year project supported by the National Institutes of Health National Institute on Drug Abuse (NIH NIDA, Award Number R01DA048009) is a prospective clinical study of opioid overdoses in the emergency department, led by Alex Manini, MD, Professor of Emergency Medicine at the Icahn School of Medicine at Mount Sinai, and a long time ToxIC collaborator. ToxIC is assessing the prevalence and role of fentalogs, novel psychoactive drugs, adulterants, and other substances in the clinical presentation and treatment of opioid overdose patients. In a supplement to this grant, ToxIC is also partnering with the Mount Sinai Health System on data collection specific to factors related to COVID-19 infections in patients with a history of opioid misuse.

Through 2021, 406 cases were entered into the ToxIC Fentalog Project, which linked clinical information with substance/illicit drug analyte information. The project has led to thirteen abstracts and one published manuscript in the *Morbidity and Mortality Weekly Report* describing co-exposure of patients with suspected opioid overdose to illicit benzodiazepines [1].

The Fentalog Project is in the process of submitting additional peer-reviewed publications this upcoming year.

ToxIC FDA ACMT COVID-19 Pharmacovigilance Project

During the COVID-19 pandemic, ToxIC and the United States Food and Drug Administration (US FDA) collaboratively implemented a real-time national toxicosurveillance project searching for adverse drug events associated with COVID-19 prophylaxis or treatment: the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project.

Through the end of 2021, the project entered 851 cases of adverse events associated with the treatment or prevention of COVID-19. The project has submitted six abstracts and produced one published manuscript describing adverse events related to ivermectin for COVID-19 prevention and treatment [2]. Project collaborators are planning to submit more peer-reviewed publications this year.

ToxIC Publications and Support

Nine full ToxIC publications were published in 2021 across four separate journals. Thirty ToxIC abstracts were published from national and international meetings. This represents the largest number of published abstracts using the ToxIC Registry to date. These full publications and abstracts are enumerated on the ToxIC website: www.toxicregistry. org.

Twenty-four new ToxIC projects were initiated in 2021. North American Snakebite Registry projects were initiated by nine investigators and Core Registry projects were initiated by fifteen investigators.

In 2021, ToxIC was supported by the NIH, US FDA, the United States Centers for Disease Control and Prevention, and BTG International, Inc. These collaborations have been enriching for ToxIC, but more importantly have provided unique networking opportunities for ToxIC investigators.

ToxIC Annual Report Highlights

In addition to summarizing the Core Registry data, this year, we are examining the distribution of new demographic variables, the continued effects of the COVID-19 pandemic on toxicologic exposures, and emerging trends in opioids and stimulants.

Methods

The ToxIC Core Registry was established on January 1, 2010 [3]. The Core Registry continues today and prospectively enrolls patients presenting to participating sites. All sites

agree to enter all inpatients and/or outpatients presenting to their site on whom a formal medical toxicology consultation was completed. ToxIC staff meet with all sites to review patient accrual, obstacles to compliance with patient entry, quality assurance efforts, and ongoing project opportunities. Deidentified case information is entered into an online data collection form using the Research Electronic Data Capture (REDCap) platform. REDCap is a secure, web-based software platform created by Vanderbilt University and designed to support data capture for research studies.

In 2021, the Core Registry collected data in the following areas:

1. Names, sites, and specific facility of the entering medical toxicologist(s)
2. Specific, focused data collection on areas of contemporary interest
3. Medication errors and adverse reactions associated with therapeutic use
4. Patient demographics
5. HIV status
6. Specific aspects of the patient's medical history
7. Source of the patient referral
8. Reasons for the patient requiring a medical toxicology consultation
9. Implicated substance(s) and their relationship, if any, to the patient's presentation
10. Patient signs and symptoms
11. Specific laboratory and electrocardiographic data
12. Treatments administered
13. Outcome
14. COVID-19 status and relatedness of exposure to COVID-19

ToxIC's data collection in 2021 included the addition of three demographic variables (marital status, housing status, and military status). This year, ToxIC also modified the race and ethnicity variables to integrate combined race-ethnicity categories. This included the addition of "Hispanic" as a race category and "Non-Hispanic White" as a separate race category. A full enumeration of all fields collected in the Core Registry is provided in the supplemental materials.

In addition to the Core Registry data collected on every bedside medical toxicology consultation, there are five detailed Sub-Registries that are completed on relevant patients. These are:

1. North American Snakebite Registry (NASBR)
2. Pediatric Marijuana and Opioid Registry
3. Extracorporeal Therapies Registry
4. Lipid Emulsion Therapy Registry
5. Natural Toxins Registry: Mushrooms and Plants

ToxIC has been reviewed by the Western Institutional Review Board and operates pursuant to the approval of the participating site IRBs. All data collected by ToxIC is deidentified and is compliant with the Health Insurance Portability and Accountability Act. All cases entered into the Core Registry, Sub-Registries, FACT Pharmacovigilance Project, and the Fentalog Project are reviewed for quality assurance by the ToxIC staff. Any inconsistent or incomplete entries are queried back to the entering medical toxicologist for correction or clarification.

Additional information regarding ToxIC can be found at https://www.toxicregistry.org.

Results

In 2021, there were a total of 8552 cases of toxicologic exposures reported to the ToxIC Core Registry from 55 health care facilities at 34 sites. This represents a 28% increase in total cases compared to 2020 [4]. Individual facilities contributing cases in 2021 are listed in Table 1. Ten new hospitals and five new cities were included in the registry in 2021.

Demographics

Tables 2, 3, and 4 summarize demographics for gender, age, and race/ethnicity, respectively. Gender breakdown was similar to previous years [4–7]. In 2021, 50.4% of cases involved female patients, and 1.4% involved transgender or gender non-conforming patients (68 female-to-male, 24 male-to-female, 24 gender non-conforming). One hundred and seven patients (1.3%) were pregnant. Age distribution was similar to previous years [3–6]. Adults 19–65 years old comprised more than half of the cases (57.1%) followed by adolescents 13–18 years old (23.4%). Children (≤ 12 years of age) made up a larger percentage compared to previous years (13%). Similar to previous years, 5.9% of cases involved older adults (> 65 years of age).

The most commonly reported race was Non-Hispanic White (54.4%), followed by Black/African (14.3%) and Hispanic (10.1%). Unknown/uncertain ethnicity was reported in 14% of cases. Race and ethnicity are self-reported by patients, or in cases in which a patient is unable to report, it may be determined by the examining medical toxicologist to the best of their ability.

Table 5 details the referral source of inpatient and outpatient medical toxicology encounters. Most (52.8%) inpatient cases were referred by the Emergency Department or admitting service (33.4%). Few cases were referred from Poison Centers (0.3%) or outpatient physicians (0.1%). Primary care and other outpatient physicians (56.7%) primarily referred outpatient consultation encounters. Self-referrals increased from 11.0% in 2020 to 28.3% in 2021 [4].

Table 1 Participating institutions providing cases to ToxIC in 2021

State or country	City	Hospitals
Arizona	Phoenix*	Banner Good Samaritan*
		Banner—University Medical Center Phoenix
		Phoenix Children's Hospital
Arkansas	Little Rock	Arkansas Children's Hospital
California	Loma Linda	Loma Linda University Medical Center
	Los Angeles	University of California Los Angeles—Olive View
		University of California Los Angeles—Ronald Reagan
		University of California Los Angeles—Santa Monica
	Sacramento	University of California Davis Medical Center
Colorado	Denver	Colorado Children's Hospital
		Denver Health Medical Center
		Porter and Littleton Hospital
		Swedish Hospital
		University of Colorado Hospital
Florida	Jacksonville*	University of Florida Health Jacksonville*
Georgia	Atlanta	Grady Memorial Hospital
Indiana	Indianapolis	Indiana University—Eskenazi Hospital
		Indiana University—Indiana University Hospital
		Indiana University—Methodist Hospital-Indianapolis
		Indiana University—Riley Hospital for Children
Kansas	Kansas City	University of Kansas Medical Center
Kentucky	Lexington	University of Kentucky Chandler Medical Center
Massachusetts	Boston*	Boston Children's Hospital
		Beth Israel Deaconess Medical Center*
	Worcester	University of Massachusetts Memorial Medical Center
Michigan	Grand Rapids	Spectrum Health Hospitals
Mississippi	Jackson	University of Mississippi Medical Center
Missouri	Kansas City	Children's Mercy Hospitals and Clinics
	St. Louis	Washington University School of Medicine in St. Louis
Nebraska	Omaha	University of Nebraska Medical Center
New Jersey	Newark	Rutgers/New Jersey Medical School
New York	Manhasset*	Staten Island University Hospital*
	Rochester	Strong Memorial Hospital
	Syracuse	Upstate Medical University—Downtown Campus
North Carolina	Charlotte	Carolinas Medical Center
Oregon	Portland	Doernbecher Children's Hospital
		Oregon Health and Science University Hospital
Pennsylvania	Bethlehem	Lehigh Valley Hospital—Cedar Crest
		Lehigh Valley Hospital—Muhlenberg
	Pittsburgh*	UPMC Mercy Hospital*
		UPMC Presbyterian/Shadyside*
	York	York Hospital
South Carolina	Greenville*	Greenville Memorial Hospital*
		Prisma Health Children's Hospital
Texas	Dallas	Children's Medical Center Dallas
		Parkland Memorial Hospital
		William P. Clements Jr University Hospital
	Houston	HCA Houston Healthcare Kingwood
Canada	Calgary	Foothills Medical Centre
		Peter Lougheed Centre
England	London*	Guy's and St Thomas' NHS Foundation Trust*

Table 1 (continued)

State or country	City	Hospitals
		St Thomas' Hospital*
Israel	Haifa*	Carmel Medical Center (IL)*
		Rambam Health Care Campus
Thailand	Bangkok	Vajira Hospital

*New participating ToxIC sites in 2021

Table 2 Patient gender and pregnancy status

	N (%)
Female	4310 (50.4)
Male	4126 (48.2)
Transgender	116 (1.4)
Female to Male	68 (58.6)[a]
Gender non-conforming	24 (20.7)[a]
Male to female	24 (20.7)[a]
Total	**8552 (100)**
Pregnant	107 (1.3)[b]

[a]Percentage based on the total number of transgender cases (N = 116)

[b]Percentage based on the total number of cases (N = 8552)

Table 3 Patient age category

	N (%)
Less than 2 years old	316 (3.7)
2–6 years old	457 (5.3)
7–12 years old	340 (4.0)
13–18 years old	1998 (23.4)
19–65 years old	4884 (57.1)
66–89 years old	502 (5.9)
Over 89 years old	17 (0.2)
Age unknown	38 (0.4)
Total	**8552 (100)**

Table 4 Patient race/ethnicity

	N (%)
American Indian/Alaskan Native	83 (1.0)
Asian	484 (5.7)
Black/African American	1227 (14.3)
Hispanic	861 (10.1)
Mixed, not otherwise specified	37 (0.4)
Native Hawaiian/Pacific Islander	7 (0.1)
Non-Hispanic White	4655 (54.4)
Race Other	5 (0.0)
Race unknown	1193 (14.0)
Total	**8552 (100)**

Tables 6 and 7 describe the primary reason for the medical toxicology encounter and details of intentional pharmaceutical exposures, respectively. Intentional pharmaceutical exposures were the most common reason for medical toxicology encounters (40.5%), similar to previous years [4–7]. Among intentional pharmaceutical exposures, most cases were again an attempt at self-harm (76.0%), primarily suicide attempts (88.7%) [4–7].

Table 8 describes data collected from three new demographic variables: marital status, military service, and housing status. Data was known regarding marital status for 57.8% of cases, military status for 46.4% of cases, and housing status for 73.8% of cases. Among cases with reported data, 70.1% were single. Military service was reported for 2.0%. Secure housing was reported in 93.4% of cases with known status.

Table 9 describes addiction medicine consultations reported in 2021. Addiction medicine consults continued to increase in frequency (6.6 to 7.1 to 9.6%) compared to previous years [4–7]. Opioid agonist therapy represented the largest percentage (72.0%) of addiction medicine consults this year.

Table 10 describes the age, gender, and race demographic distribution of COVID-19-positive cases entered into ToxIC. Of those tested for COVID-19, 178 cases (2.1%) were COVID-19 positive and 4422 (51.7%) were COVID-19 negative, with the remaining 3952 (46.2%) having unknown COVID-19 status. Most COVID-19 positive cases were adults ages 19–65 years old (60.1%) or adolescents ages 13–18 years old (21.9%). Males represented 48.3% of cases. Most COVID-19-positive cases were non-Hispanic White (52.3%), followed by Black/African American (18.5%) and Hispanic (15.7%). There were three COVID-19 positive ToxIC case fatalities (1.7%).

Agent Classes

Agent class contributions to the Core Registry are described in Table 11. The total number of agent classes reported was 11,793. Of the 8552 cases entered into the registry in 2021, 7884 included at least one specific agent of exposure. Single agents were involved in 5541 cases. Consistent with previous years, the non-opioid analgesic class was the most common class of drugs reported (14.9%), but the proportion

Table 5 Case referral sources by inpatient/outpatient status

	N (%)
Emergency Department (ED) or inpatient (IP)[a]	
ED	4485 (52.8)
Admitting service	2838 (33.4)
Request from another hospital service (not ED)	641 (7.5)
Outside hospital transfer	385 (4.5)
Self-referral	105 (1.2)
Poison Center	28 (0.3)
Primary care provider or other outpatient treating physician	7 (0.1)
Employer/independent medical evaluation	3 (0.0)
Total	**8492 (99.8)**
Outpatient (OP)/clinic/office consultation[b]	
Primary care provider or other OP physician	34 (56.7)
Self-referral	17 (28.3)
Employer/Independent medical evaluation	5 (8.3)
ED	4 (6.7)
Admitting service	0 (0.0)
Outside hospital transfer	0 (0.0)
Poison Center	0 (0.0)
Request from another hospital service (not ED)	0 (0.0)
Total	**60 (100)**

[a]Percentage based on the total number of cases (N=8492) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP)

[b]Percentage based on the total number of cases (N=60) seen by a medical toxicologist as outpatient, clinic visit, or office consultation

decreased slightly from the previous year (15.5% in 2020) [4]. The opioid class was the second most common agent class reported (13.1%) and increased from the previous year (12.7% in 2020) [4].

Agent Classes and COVID-19

Table 12 describes the primary agent exposure classes for COVID-19-positive cases. Opioids represented the largest agent class (18.3%) followed by analgesics (16.5%), alcohol ethanol (11.8%), antidepressants (9.9%), and sympathomimetics (9.9%).

Table 13 describes the primary agent exposure classes for exposures related to a patient's COVID-19 status. Toxicologists were asked if they believed that the patient's toxic exposure was related to their COVID-19 status. Agent classes that toxicologists most commonly associated with patient COVID-19 status included analgesics (14.4%), opioids (13.6%), and alcohol ethanol (12.0%).

Analgesics

Table 14 presents the non-opioid analgesics, the largest class in the Core Registry, containing 1753 exposures. Acetaminophen was again the most commonly reported agent (62.9%) and continues to be the highest reported drug of

exposure annually since ToxIC was established [4–7]. It is again distantly followed by ibuprofen (13.3%), gabapentin (6.9%), and aspirin (5.6%). Aspirin and acetylsalicylic acid are listed separately in the registry; when combined, they compose 9.6% of the non-opioid analgesic class.

Opioids

Table 15 describes the opioid class. This year, fentanyl (40.1%) was the most common opioid agent class, overtaking heroin (20.6%) for the first time in the history of the ToxIC annual report. The relative contribution of fentanyl has been steadily increasing from previous years and represented only 25.4% of the opioid class in 2020 [4]. Oxycodone was the third most common agent reported again this year (11.7%) [4].

Antidepressants

Table 16 describes the antidepressant class. Selective serotonin reuptake inhibitors (SSRIs) (42.1%) and other antidepressants (39.2%) represented most of this class. Sertraline (16.1%) was the most common SSRI reported and bupropion (23.7%) was the most common other antidepressant, similar to previous years [4–7]. Tricyclic antidepressants were only 8.1% of reported cases.

Table 6 Reason for medical toxicology encounter

	N (%)[a]
Intentional exposure—pharmaceutical	3958 (40.5)
Intentional exposure—non-pharmaceutical	1002 (10.2)
Addiction medicine consultation	942 (9.6)
Withdrawal—ethanol	803 (8.2)
Unintentional exposure—pharmaceutical	625 (6.4)
Withdrawal—opioid	463 (4.7)
Ethanol abuse	442 (4.5)
Unintentional exposure—non-pharmaceutical	427 (4.4)
Organ system dysfunction	350 (3.6)
Envenomation—snake	315 (3.2)
Interpretation of toxicology lab data	154 (1.6)
Withdrawal—sedative/hypnotic	68 (0.7)
Environmental evaluation	67 (0.7)
Envenomation—other	48 (0.5)
Envenomation—spider	44 (0.5)
Withdrawal—other	21 (0.2)
Occupational evaluation	19 (0.2)
Malicious/criminal	12 (0.1)
Withdrawal—cocaine/amphetamine	8 (0.1)
Envenomation—scorpion	5 (0.1)
Marine/fish poisoning	3 (0.0)
Total	**9776 (100)**

[a]Percentages based on total number of reasons for toxicology encounter. Case entries may include more than one reason for a medical toxicology encounter

Table 7 Detailed reason for encounter—intentional pharmaceutical exposure[a]

	N (%)
Reason for intentional pharmaceutical exposure subgroup[b]	
Attempt at self-harm	3009 (76.0)
Misuse/abuse	415 (10.5)
Therapeutic use	294 (7.4)
Unknown	240 (6.1)
Total	**3958 (100)**
Attempt at self-harm—suicidal intent subclassification[c]	
Suicidal intent	2668 (88.7)
Suicidal intent unknown	239 (7.9)
No suicidal intent	102 (3.4)
Total	**3009 (100)**

[a]Thirty-two cases listed more than one reason for encounter due to intentional pharmaceutical exposure (N=3926)

[b]Percentage based on total number indicating reason for encounter due to intentional pharmaceutical exposure

[c]Percentage based on number of cases indicating attempt at self-harm

Sedative Hypnotics

Table 17 presents the sedative hypnotic/muscle relaxant class. Benzodiazepines represented the majority of the class

Table 8 New demographic variables

	N (%)
Marital status	
Unknown/missing	3607 (42.2)
Total reported marital status	**4945 (57.8)**
Married	994 (20.1)[a]
Divorced	419 (8.5)[a]
Single	3468 (70.1)[a]
Widowed	64 (1.3)[a]
Military service	
Unknown/missing	4585 (53.6)
Total reported military status	**3967 (46.4)**
Yes, previous military service	78 (2.0)[b]
No previous military service	3889 (98.0)[b]
Housing status	
Unknown/missing	2241 (26.2)
Total reported housing status	**6311 (73.8)**
Secured housing	5894 (93.4)[c]
Undomiciled	365 (5.8)[c]
Other	52 (0.8)[c]

[a]Percentage based on reported cases (N=4945)

[b]Percentage based on reported cases (N=3967)

[c]Percentage based on reported cases (N=6311)

Table 9 Addiction medicine consultations

	N (%)
Alcohol dependence pharmacotherapy	35 (6.0)
Counseling and support only	64 (11.0)
Opioid agonist therapy	417 (72.0)
Opioid antagonist therapy	18 (3.1)
Pain management	46 (7.9)
Total	**580 (100)**

(58.8%), followed by muscle relaxants (23.8%). Among benzodiazepines, alprazolam (22.4%) and clonazepam (15.3%) were the most common sub-types. Among muscle relaxants, baclofen (11.0%) and cyclobenzaprine (7.1%) were the most common sub-types, similar to previous years [4–7]. Other sedatives, Z-drugs, and barbiturates were less common.

Ethanol and Toxic Alcohols

Table 18 describes data on ethanol and toxic alcohols. Ethanol was considered its own agent class, consistent with prior years, and was the third most commonly reported agent class (up from fourth in 2020) [4]. The most commonly reported nonethanol alcohols and glycols were isopropanol (36.9%), ethylene glycol (29.2%), and methanol (15.4%).

Table 10 Demographic variable distribution for COVID-19-positive cases

	N (%)[a]
Age category	
Less than 2 years old	6 (3.4)
2–6 years old	5 (2.8)
7–12 years old	8 (4.5)
13–18 years old	39 (21.9)
19–65 years old	107 (60.1)
66–89 years old	11 (6.2)
Over 89 years old	2 (1.1)
Age unknown	0 (0.0)
Gender	
Female	86 (48.3)
Male	86 (48.3)
Transgender	6 (3.4)
Race/ethnicity	
American Indian/Alaskan Native	2 (1.1)
Asian	6 (3.4)
Black/African American	33 (18.5)
Hispanic	28 (15.7)
Mixed, not otherwise specified	1 (0.6)
Native Hawaiian/Pacific Islander	0 (0.0)
Non-Hispanic White	93 (52.3)
Race Other	0 (0.0)
Race Unknown	15 (8.4)

[a]Percentages based on COVID-19-positive patients only ($N = 178$)

Sympathomimetics

Table 19 presents the sympathomimetic class. Methamphetamine (43.2%) was the most common agent in this class and increased from 40.3% in 2020 [4]. Cocaine (26.8%) was the second most common agent in this class, followed by amphetamine (10.2%).

Anticholinergic/Antihistamine

Table 20 describes the anticholinergic/antihistamine class. Consistent with previous years, diphenhydramine (53.2%), followed by hydroxyzine (20.8%), was the most commonly reported agent in this class [4–7].

Cardiovascular Agents

Table 21 shows data on the cardiovascular class. Consistent with previous years, sympatholytic alpha-2 agonists (31.6%) remain the most common sub-class of cardiovascular drugs, followed by beta-blockers (22.2%) and calcium channel blockers (15.0%) [4–7]. Clonidine

Table 11 Agent classes involved in medical toxicology consultation

	N (%)[a]
Analgesic	1753 (14.9)
Opioid	1546 (13.1)
Ethanol	1259 (10.7)
Antidepressant	1239 (10.5)
Sympathomimetic	826 (7.0)
Sedative-hypnotic/muscle relaxant	799 (6.8)
Anticholinergic/antihistamine	713 (6.0)
Cardiovascular	693 (5.9)
Antipsychotic	507 (4.3)
Psychoactive	422 (3.6)
Envenomation	376 (3.2)
Anticonvulsant	305 (2.6)
Herbal products/dietary supplements	143 (1.2)
Diabetic medication	129 (1.1)
Lithium	110 (0.9)
Cough and cold products	96 (0.8)
Caustic	95 (0.8)
Gases/irritants/vapors/dusts	88 (0.7)
Household products	86 (0.7)
Unknown class	76 (0.6)
Toxic alcohols	65 (0.6)
Antimicrobials	59 (0.5)
Metals	56 (0.5)
GI	44 (0.4)
Plants and fungi	43 (0.4)
Hydrocarbon	35 (0.3)
Endocrine	32 (0.3)
Chemotherapeutic and immune	32 (0.3)
Anesthetic	26 (0.2)
Other pharmaceutical product	26 (0.2)
Anticoagulant	25 (0.2)
Other nonpharmaceutical product	19 (0.2)
Insecticide	17 (0.1)
Amphetamine-like hallucinogen	12 (0.1)
Anti-parkinsonism drugs	9 (0.1)
Pulmonary	9 (0.1)
Herbicide	7 (0.1)
Rodenticide	6 (0.0)
WMD[b]/riot agent/radiological	5 (0.0)
Ingested foreign body	2 (0.0)
Marine toxin	2 (0.0)
Cholinergic	1 (0.0)
Total agents	**11,793 (100)**

[a]Percentages based on total number of reported agent entries from 7884 cases; 5541 cases (70.3%) reported single agents

[b]*WMD* weapon of mass destruction

(23.5%) was the most common sympatholytic, while propranolol (8.7%) was the most common beta-blocker agent this year. Propranolol overtook metoprolol as the most common beta-blocker agent this year. Amlodipine

Table 12 Agent class exposures for COVID-19-positive cases

	N (%)[a]
Alcohol ethanol	25 (11.8)
Alcohol toxic	2 (0.9)
Analgesic	35 (16.5)
Anticholinergic	10 (4.7)
Anticonvulsant	3 (1.4)
Antidepressant	21 (9.9)
Antipsychotic	11 (5.2)
Cardiovascular	7 (3.3)
Caustic	1 (0.5)
Cough and cold	3 (1.4)
Diabetic	2 (0.9)
Envenomation	4 (1.9)
Gases and vapors	1 (0.5)
GI	1 (0.5)
Herbals	1 (0.5)
Household	1 (0.5)
Insecticide	1 (0.5)
Lithium	4 (1.9)
Metals	1 (0.5)
Opioids	39 (18.3)
Other non-pharmaceutical	1 (0.5)
Plants and fungi	1 (0.5)
Psychoactive	2 (0.9)
Sed-hypnotics	12 (5.7)
Sympathomimetics	21 (9.9)
Unknown	2 (0.9)
Total agents reported	**212 (100)**

[a]Percentages based on total number of reported agent entries in 2021 from COVID-19-positive patients (N = 178)

Table 13 Agent class exposures for which exposure was related to COVID-19 status

	N (%)[a]
Alcohol ethanol	15 (12.0)
Amphetamines	1 (0.8)
Analgesic	18 (14.4)
Anticholinergic	6 (4.8)
Anticonvulsant	4 (3.2)
Antidepressant	13 (10.4)
Antipsychotic	3 (2.4)
Cardiovascular	7 (5.6)
Caustic	1 (0.8)
Cough and cold	2 (1.6)
Diabetic	1 (0.8)
Envenomation	2 (1.6)
Gases and vapors	1 (0.8)
GI	1 (0.8)
Herbals	1 (0.8)
Household	2 (1.6)
Insecticide	3 (2.4)
Lithium	1 (0.8)
Opioids	17 (13.6)
Rodenticide	1 (0.8)
Psychoactive	4 (3.2)
Sed-hypnotics	9 (7.2)
Sympathomimetics	10 (8.0)
Unknown	2 (1.6)
Total agents reported	**125 (100)**

[a]Percentages based on total number of reported agent entries from patients for whom the toxicologist answered that their exposure was related to their COVID-19 status (N = 92)

(10.4%) remained the most common calcium channel blocker.

Antipsychotics

Table 22 details the antipsychotic class. Trends in the antipsychotic class were similar to previous years [4–7]. The atypicals, led by quetiapine (40.2%) and olanzapine (14.6%), were the most commonly reported antipsychotic agents.

Anticonvulsants, Mood Stabilizers, and Lithium

Table 23 presents data on anticonvulsants, mood stabilizers, and lithium. Lithium was considered its own agent class and made up 1.3% of reported agents in the Core Registry [4–7]. Among anticonvulsants and mood stabilizers, lamotrigine (30.5%) and valproic acid (22.0%) were the most commonly reported agents, followed by oxcarbazepine (11.8%) and topiramate (7.9%).

Table 14 Analgesics

	N (%)
Acetaminophen	1103 (62.9)
Ibuprofen	233 (13.3)
Gabapentin	121 (6.9)
Aspirin	99 (5.6)
Acetylsalicylic acid	70 (4.0)
Naproxen	41 (2.3)
Pregabalin	19 (1.1)
Salicylic acid	19 (1.1)
Paracetamol	12 (0.7)
Meloxicam	11 (0.6)
Diclofenac	6 (0.3)
Methylsalicylate	5 (0.3)
Miscellaneous[a]	14 (0.8)
Class total	**1753 (100)**

[a]Includes analgesic unspecified, indomethacin, ketorolac, mefenamic acid, metamizole (dipyrone), nabumetone, non-steroidal anti-inflammatory drug (NSAID) unspecified, piroxicam, and salsalate

Table 15 Opioids

	N (%)
Fentanyl	620 (40.1)
Heroin	319 (20.6)
Oxycodone	180 (11.7)
Buprenorphine	104 (6.7)
Methadone	79 (5.1)
Opioid unspecified	74 (4.8)
Tramadol	63 (4.1)
Hydrocodone	33 (2.1)
Morphine	22 (1.4)
Codeine	15 (1.0)
Naloxone	9 (0.6)
Naltrexone	6 (0.4)
Miscellaneous[a]	22 (1.4)
Class total	**1546 (100)**

[a]Includes acetyl fentanyl, bucinnazine (AP 237, 1-butyryl-4-cinnamylpiperazine), depropionylfentanyl, dihyrocodeine, diphenoxylate, fluorofentanyl, hydromorphone, loperamide, meperidine, methylfentanyl (3- or alpha), N-piperidinyl etonitazene, oxymorphone, and tapentadol

Psychoactives

Table 24 presents data on the psychoactive class including the amphetamine-like hallucinogen methylenedioxymethamphetamine (Molly). Marijuana was again the most common agent in this class (26.1%) followed by delta-9 tetrahydrocannabinol (17.8%). Synthetic cannabinoid cases continued to fall this year (5.0% in 2021 vs 5.6% in 2020 and 9.4% in 2019) [4–7]. Molly exposures, which is considered its own agent class, remained low with 12 cases reported.

Envenomations and Marine Poisonings

Table 25 shows data on envenomations and marine poisonings. Snake envenomations represented by Crotalus (23.9%), and Agkistrodon (23.9%) were the top two known snake exposures reported to this class. Unspecified snake envenomations comprised a large proportion of envenomations (29.7%), including pit viper unspecified (16.2%) and snake unspecified (13.6%). Loxosceles exposures were the fifth most common exposure in this class (6.1%).

Diabetic Medications

Table 26 presents the diabetic medication agent class. Metformin was the most common agent (38.8%), followed by

Table 16 Antidepressants

	N (%)
Selective serotonin reuptake inhibitors (SSRIs)	**522 (42.1)**
Sertraline	200 (16.1)
Fluoxetine	132 (10.7)
Escitalopram	110 (8.9)
Citalopram	47 (3.8)
Paroxetine	21 (1.7)
Fluvoxamine	8 (0.6)
Vilazodone	4 (0.3)
Other antidepressants	**486 (39.2)**
Bupropion	294 (23.7)
Trazodone	143 (11.5)
Mirtazapine	43 (3.5)
Miscellaneous[a]	4 (0.3)
Antidepressant unspecified	2 (0.2)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	**131 (10.6)**
Venlafaxine	69 (5.6)
Duloxetine	55 (4.4)
Desvenlafaxine	7 (0.6)
Tricyclic Antidepressants (TCAs)	**100 (8.1)**
Amitriptyline	79 (6.4)
Doxepin	8 (0.6)
Nortriptyline	6 (0.5)
Miscellaneous[b]	7 (0.6)
Class total	**1239 (100)**

[a]Includes vortioxetine, agamelatine, mianserin

[b]Includes imipramine, clomipramine, amoxapine, melitracen

glipizide (22.5%). Insulin composed 17.1% of reported cases.

Metals

Table 27 presents the metal class. Lithium is reported with the anticonvulsants and mood stabilizers. Iron (37.5%) and lead (33.9%) composed the majority of reported cases. Iron cases increased from 28.2% in 2020 [4]. Mercury was reported in 5 cases (8.9%).

Herbal Products and Dietary Supplements

Table 28 details herbal products and dietary supplements. Caffeine (30.0%) and melatonin (29.4%) made up the majority of this class. Miscellaneous agents with less frequently reported agents composed 35.7% of the agent class.

Table 17 Sedative-hypnotic/muscle relaxants by type

	N (%)
Benzodiazepine	**470 (58.8)**
Alprazolam	179 (22.4)
Clonazepam	122 (15.3)
Lorazepam	72 (9.0)
Benzodiazepine unspecified	40 (5.0)
Diazepam	39 (4.9)
Temazepam	8 (1.0)
Miscellaneous[a]	10 (1.3)
Muscle Relaxant	**190 (23.8)**
Baclofen	88 (11.0)
Cyclobenzaprine	57 (7.1)
Tizanidine	31 (3.9)
Methocarbamol	11 (1.4)
Miscellaneous[b]	3 (0.4)
Other sedatives	**69 (8.6)**
Buspirone	42 (5.3)
Sed-hypnotic/muscle relaxant unspecified	9 (1.1)
Phenibut (beta-phenyl-gamma-aminobutyric acid)	5 (0.6)
Miscellaneous[c]	13 (1.6)
Non-benzodiazepine agonists ("Z" drugs)	**54 (6.8)**
Zolpidem	44 (5.5)
Eszopiclone	6 (0.8)
Miscellaneous[d]	4 (0.5)
Barbiturates	**16 (2.0)**
Phenobarbital	6 (0.8)
Butalbital	5 (0.6)
Miscellaneous[e]	5 (0.6)
Class total	**799 (100)**

[a]Includes chlordiazepoxide, clorazepate, triazolam, phenazepam, midazolam, flubromazepam, and flualprazolam

[b]Includes carisoprodol and eperisone

[c]Includes propofol, orphenadrine, aminobutyric acid, zolazepam, ramelteon, chloral hydrate, and brotizolam

[d]Includes zopiclone and zaleplon

[e]Includes barbituate unspecified, pentobarbital, and butabarbital

Table 18 Ethanol and toxic alcohols

	N (%)
Ethanol[a]	**1259 (100)**
Nonethanol alcohols and glycols	
Isopropanol	24 (36.9)
Ethylene glycol	19 (29.2)
Methanol	10 (15.4)
Propylene Glycol	4 (6.2)
Acetone	3 (4.6)
Glycol ethers	1 (1.5)
Propylene glycol butyl ether	1 (1.5)
Dipropylene glycol	1 (1.5)
Diethylene glycol	1 (1.5)
Toxic alcohol unspecified	1 (1.5)
Class total	**65 (100)**

[a]Ethanol is considered a separate agent class

Table 19 Sympathomimetic agents.

	N (%)
Methamphetamine	356 (43.2)
Cocaine	221 (26.8)
Amphetamine	84 (10.2)
Methylphenidate	48 (5.8)
Dextroamphetamine	35 (4.2)
Lisdexamfetamine	20 (2.4)
MDMA (methylenedioxy-N-methamphetamine, ecstasy)	14 (1.7)
Dexmethylphenidate	12 (1.5)
Atomoxetine	10 (1.2)
Phentermine	6 (0.7)
Sympathomimetic unspecified	5 (0.6)
Phenylephrine	5 (0.6)
Miscellaneous[a]	8 (1.0)
Class total	**824 (100)**

[a]Includes pseudoephedrine, clenbuterol, phenylpropanolamine, and benzphetamine

Household Products

Table 29 describes household products reported to the Core Registry. Cleaning solutions and disinfectants (23.3%) and sodium hypochlorite $\leq 6\%$ (23.3%) were the most commonly reported agents in this class. Laundry detergent pod exposures decreased from 19.7% in 2020 to 11.6% in 2021 [4].

Gases, Irritants, Vapors, and Dusts

Table 30 presents data for the gases, irritants, vapors, and dust class. Carbon monoxide (57.5%) represented the majority of cases in this class.

Cough and Cold Preparations

Table S1 details data on cough and cold preparations reported to the Core Registry. Dextromethorphan was again the most commonly reported agent, making up 68.8% of the class [4–7].

Caustics

Table S2 presents the caustic agent class. Sodium hypochlorite (concentration unknown) was the most common agent reported in this class (17.9%), followed by sodium hydroxide (15.8%).

Table 20 Anticholinergics and antihistamines

	N (%)
Diphenhydramine	379 (53.2)
Hydroxyzine	148 (20.8)
Cetirizine	26 (3.6)
Doxylamine	24 (3.4)
Chlorpheniramine	23 (3.2)
Benztropine	18 (2.5)
Loratadine	16 (2.2)
Pyrilamine	14 (2.0)
Promethazine	14 (2.0)
Cyproheptadine	10 (1.4)
Trihexyphenidyl	8 (1.1)
Dicyclomine	6 (0.8)
Dimenhydrinate	5 (0.7)
Miscellaneous[a]	22 (3.1)
Class total	**713 (100)**

[a]Includes antihistamine unspecified, hyoscyamine, fexofenadine, scopolamine, meclizine, desloratadine, brompheniramine, atropine, levocetirizine, oxybutynin, chlorcyclizine

Antimicrobials

Table S3 presents data on antimicrobial agents. Antibiotics were the most common sub-class (78.0%), with dapsone (15.3%), amoxicillin (8.5%), and miscellaneous antibiotics (54.2%) included in this class. Antivirals (11.9%) and other antimicrobials (10.2%) were less common.

Plants and Fungi

Table S4 describes plant and fungi exposures reported to the Core Registry. In 2021, mitragyna speciosa (kratom) was the most common single exposure (32.6%) and increased from 16.3% in 2020 [4]. Psilocybin exposure (16.3%) was the second most common exposure sub-type. Infrequent miscellaneous agents contributed to the majority of this class (37.2%).

Hydrocarbons

Table S5 describes the hydrocarbon agent class. Infrequent miscellaneous agents represented the majority (71.4%) of the class. This year, the largest single agent contributor was Tiki torch fuel (17.1%).

Table 21 Cardiovascular agents by type

	N (%)
Alpha-2 agonist	**219 (31.6)**
Clonidine	163 (23.5)
Guanfacine	54 (7.8)
Miscellaneous[a]	2 (0.3)
Beta blockers	**154 (22.2)**
Propranolol	60 (8.7)
Metoprolol	52 (7.5)
Carvedilol	22 (3.2)
Atenolol	6 (0.9)
Miscellaneous[b]	14 (2.0)
Calcium channel blocker	**104 (15.0)**
Amlodipine	72 (10.4)
Diltiazem	12 (1.7)
Verapamil	11 (1.6)
Nifedipine	9 (1.3)
Other antihypertensives and vasodilators	**61 (8.8)**
Prazosin	43 (6.2)
Hydralazine	8 (1.2)
Miscellaneous[c]	10 (1.4)
ACEI/ARB	**55 (7.9)**
Lisinopril	31 (4.5)
Losartan	15 (2.2)
Miscellaneous[d]	9 (1.3)
Diuretics	**36 (5.2)**
Hydrochlorothiazide	19 (2.7)
Spironolactone	7 (1.0)
Furosemide	5 (0.7)
Miscellaneous[e]	5 (0.7)
Cardiac glycosides	**27 (3.9)**
Digoxin	26 (3.8)
Digitoxin	1 (0.1)
Antidysrhythmics and other CV agents	**19 (2.7)**
Flecainide	7 (1.0)
Miscellaneous[f]	12 (1.7)
Antihyperlipidemic	**18 (2.6)**
Atorvastatin	10 (1.4)
Miscellaneous[g]	8 (1.2)
Class total	**693 (100)**

[a]Includes xylazine and dexmedetomidine

[b]Includes nebivolol, nadolol, labetalol, bisoprolol, and acebutolol

[c]Includes tamsulosin, isosorbide, terazosin, nitroprusside, isobutyl nitrite, doxazosin, and antihypertensive unspecified

[d]Includes valsartan, enalapril, perindopril, fosinopril, sacubitril and candesartan

[e]Includes chlorthalidone, bumetanide, and acetazolamide

[f]Includes sotalol, quinidine, propafenone, cardiovascular agent unspecified, amiodarone, and midodrine

[g]Includes simvastatin, pravastatin, fenofibrate, and ezetimibe

Table 22 Antipsychotics

	N (%)
Quetiapine	204 (40.2)
Olanzapine	74 (14.6)
Aripiprazole	59 (11.6)
Risperidone	56 (11.0)
Haloperidol	35 (6.9)
Ziprasidone	15 (3.0)
Clozapine	14 (2.7)
Chlorpromazine	12 (2.3)
Lurasidone	8 (1.5)
Prochlorperazine	6 (1.2)
Paliperidone	5 (1.0)
Miscellaneous[a]	19 (4.0)
Class total	**507 (100)**

[a]Includes fluphenazine, perphenazine, cariprazine, brexpiprazole, antipsychotic unspecified, droperidol, flupentixol, loxapine, iloperidone, and trifluoperazine

Table 23 Anticonvulsants and mood stabilizers

	N (%)
Lithium[a]	110 (100.0)
Other anticonvulsants/mood stabilizers	
Lamotrigine	93 (30.5)
Valproic acid	67 (22.0)
Oxcarbazepine	36 (11.8)
Topiramate	24 (7.9)
Carbamazepine	21 (6.9)
Phenytoin	18 (5.9)
Levetiracetam	15 (4.9)
Divalproex	13 (4.3)
Lacosamide	8 (2.6)
Zonisamide	5 (1.6)
Miscellaneous[b]	5 (1.6)
Class total	**305 (100)**

[a]Lithium is considered a separate agent class

[b]Includes clobazam and etifoxine

Gastrointestinal Agents

Table S6 presents gastrointestinal agents. Omeprazole (25.0%), ondansetron (18.2%), pantoprazole (9.1%), and metoclopramide (9.1%) were the most commonly reported agents.

Table 24 Psychoactives

	N (%)
Molly-amphetamine-like hallucinogen[a]	12 (100.0)
Other psychoactives	
Marijuana	110 (26.1)
Delta-9-tetrahydrocannabinol	75 (17.8)
Tetrahydrocannabinol	69 (16.4)
Cannabinoid nonsynthetic	46 (10.9)
Cannabinoid synthetic	21 (5.0)
Nicotine	17 (4.0)
Ketamine	16 (3.8)
Gamma hydroxybutyrate	16 (3.8)
Cannabidiol	14 (3.3)
Phencyclidine	10 (2.4)
LSD[b]	8 (1.9)
Methylenedioxymethamphetamine	6 (1.4)
Miscellaneous[c]	14 (5.6)
Class total	**306 (100)**

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

[b]*LSD* lysergic acid diethylamide

[c]Includes delta-8-tetrohyrdrocannabinol, 1,4 butanediol, 3-methoxyphencyclidine, 2-fluorodeschlorketamine, gamma butyrolactone, 2,6-dimethoxy-4-methylamphetamine (DOM, STP), pharmaceutical THC, varencicline, dimethyltryptamine (DMT), tiletamine

Table 25 Envenomations

	N (%)
Crotalus (rattlesnake)	90 (23.9)
Agkistrodon (copperhead, cottonmouth/water moccasin)	90 (23.9)
Trimeresurus unspecified (pit viper unspecified)	61 (16.2)
Snake unspecified	51 (13.6)
Loxosceles (recluse spiders)	23 (6.1)
Animal bite unspecified	22 (5.9)
Chilopoda (centipede unspecified)	12 (3.2)
Latrodectus (widow spiders)	7 (1.9)
Scorpion unspecified	5 (1.3)
Miscellaneous[a]	15 (4.0)
Class total	**376 (100)**

[a]Includes spider unspecified, Hymenoptera (Bees, Wasps, Ants), *Vipera palaestinae*, Micrurus (coral snake eastern), Naja unspecified (cobra spp unknown), Envenomation unspecified, *Bitis nasicornis* (butterfly or rhinoceros viper), and *Atheris squamigera* (green bush, variable bush, or leaf viper)

Pesticide Agents (Insecticides, Herbicides, Rodenticides, and Fungicides)

Table S7 presents the pesticide (insecticide, herbicide, rodenticide, and fungicide) class. There were seven herbicides reported (23.3%), with glyphosate being the most

Table 26 Diabetic medications

	N (%)
Metformin	50 (38.8)
Glipizide	29 (22.5)
Insulin	22 (17.1)
Glimepiride	22 (17.1)
Glyburide	5 (3.9)
Miscellaneous[a]	13 (10.1)
Class total	**129 (100)**

[a]Includes dapagliflozin, diabetic medication unspecified, dulaglutide, ertugliflozin, linagliptin, pioglitazone, semaglutide, sitagliptin, and sulfonylurea unspecified

Table 27 Metals

	N (%)
Iron	21 (37.5)
Lead	19 (33.9)
Mercury	5 (8.9)
Miscellaneous[a]	11 (19.7)
Class total	**56 (100)**

[a]Includes gadolinium, zinc metal, steel iron unspecified, silver, cobalt, chromium, cadmium, beryllium, arsenic, and aluminum

Table 28 Herbal products and dietary supplements

	N (%)
Caffeine	43 (30.0)
Melatonin	42 (29.4)
Vitamin D	7 (4.9)
Miscellaneous[a]	51 (35.7)
Class total	**143 (100)**

[a]Includes 5-hydroxytryptophan, alpha lipoic acid, arginine, ashwangandha, calcium, chicory, electrolyte supplement unspecified, eucalyptus oil, Ginkgo biloba, herbal (dietary) multibotanical, herbals/dietary supplements/vitamins unspecified, limonene, maca powder, menthol, methylxanthine, multiple vitamin, potassium, Saint John's wort, sodium chloride, tea tree oil, vitamin A, vitamin B1 (thiamine), vitamin B3 (niacin), vitamin B9 (folic acid), vitamin C (ascorbic acid), yohimbine, and zinc

Table 29 Household products

	N (%)
Cleaning solutions and disinfectants	20 (23.3)
Sodium hypochlorite ≤ 6%	20 (23.3)
Laundry detergent pod	10 (11.6)
Soaps and detergents	7 (8.1)
Miscellaneous[a]	29 (33.7)
Class total	**86 (100)**

[a]Includes ammonia < 10%, aromatic or essential oils (carrier/solvent base unspecified), corn starch, degreaser, dishwasher detergent, dishwasher detergent pod, drain cleaner (irritant), fabric starch, fire extinguisher (purple K), hair product, hand sanitizer unspecified, household product unspecified, mouthwash, nail polish, oven cleaner, perfume, pool sealant, and window or glass cleaner unspecified

Table 30 Gases, irritants, vapors and dusts

	N (%)
Carbon monoxide	50 (57.5)
Chlorine	14 (16.1)
Cyanide	5 (5.7)
Miscellaneous[a]	18 (20.7)
Class total	**87 (100)**

[a]Includes gases/vapors/irritants/dusts unspecified, smoke, phosgene, vaping NOS, fumes/vapors/gases unspecified, chloramine, duster (canned air), nitric oxide, chlorine dioxide, petroleum vapors, flame retardant unspecified

common. There were 17 (56.7%) insecticides and 6 (20.0%) rodenticides reported. Again, no fungicides were reported.

Chemotherapeutic and Immunological Agents

Table S8 describes chemotherapeutic and immunological agents. Methotrexate (25.0%), hydroxychloroquine (25.0%), and azathioprine (9.4%) were the three most commonly reported agents. Hydroxychloroquine exposures increased from 13.3% in 2020 [4].

Anticoagulants

Table S9 details anticoagulant class exposures. Warfarin (36.0%) was again the most common agent reported [4–7].

Anesthetics

Table S10 describes the anesthetic class exposures reported in 2021. Benzonatate (30.8%) and lidocaine (26.9%) were the most commonly reported agents.

Other Pharmaceuticals

Table S11 presents the other pharmaceutical products agent class. Most of the class (61.5%) was made up of miscellaneous agents. Hydrogen peroxide < 10% was the most commonly reported single agent (15.4%).

Endocrine

Table S12 describes the 32 endocrine agents reported. Levothyroxine represented more than half of the reported agents (53.1%).

Other Non-pharmaceuticals

Table S13 describes the other non-pharmaceutical class. Quaternary ammonium (10.5%), surfactant (10.5%), and acrylates unspecified (10.5%) were the three most common agents reported.

Pulmonary Agents

Table S14 describes reported pulmonary agents. Montelukast was again the most common agent reported (88.9%) [4–7].

Foreign Bodies

Table S15 details the foreign object ingestions reported to the Core Registry. Two agents were reported: screws and slime unspecified. No battery ingestions were reported in the Core Registry.

Anti-Parkinsonism Agents

Table S16 presents the anti-parkinsonism agent class, containing nine entries. Ropinirole was the most commonly reported agent (44.5%). Other reported agents included pramipexole, levodopa/carbidopa, and selegiline.

Weapons of Mass Destruction

Botulinum toxin (five cases) was the only agent reported in the class of weapons of mass destruction, described in Table S17.

Cholinergics

Table S18 describes the single cholinergic/parasympathetic agent reported, cholinergic/parasympathetic unspecified.

Chelators

There were no chelator agent exposures reported in 2021.

Clinical Signs and Symptoms

The categories of clinical signs and symptoms describe a diverse range of abnormal clinical findings. Questions about clinical signs are mandatory in the Registry and there are no missing entries for this subsection. Predefined criteria must be met for each category for a sign or symptom to be reported as present. 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 and their individual signs and symptoms are calculated relative to the total number of Core Registry cases ($N = 8552$) and it is possible for the total to be greater than 100%.

Toxidromes

Table 31 reports the 2331 toxidromes reported to the Core Registry in 2021. Consistent with previous years, the sedative-hypnotic toxidrome was the most common (6.9% in 2021) but decreased from previous years (8.3% in 2020) [4]. The opioid toxidrome increased again this year (5.4% in 2021, 3.7% in 2020) [4]. The anticholinergic toxidrome (5.0%) was the third most common toxidrome reported.

Major Vital Sign Abnormalities

Table 32 presents the 2082 vital sign abnormalities reported to the Core Registry in 2021. Trends were nearly identical to previous years [4–7]. Tachycardia (10.0%), hypotension (5.5%), and bradycardia (3.2%) were the most common vital sign abnormalities reported.

Table 31 Toxidromes

	N (%)[a]
No toxidrome reported	6221 (72.7)
Total reported toxidromes	**2331 (27.3)**
Sedative-hypnotic	587 (6.9)
Opioid	461 (5.4)
Anticholinergic	426 (5.0)
Sympathomimetic	309 (3.6)
Serotonin syndrome	230 (2.7)
Alcoholic ketoacidosis	177 (2.1)
Sympatholytic	66 (0.8)
Washout syndrome	28 (0.3)
Cannabinoid hyperemesis	15 (0.2)
NMS[b]	11 (0.1)
Cholinergic	8 (0.1)
Overlap syndromes	6 (0.1)
Anticonvulsant hypersensitivity	6 (0.1)
Fume fever	1 (<0.1)

[a]Percentage based on the number cases reporting specific toxidrome relative to total number of registry cases in 2021 ($N=8552$)

[b]*NMS* neuroleptic malignant syndrome

Table 32 Major vital sign abnormalities

	N (%)[a]
Total unique cases with 1 + major vital sign abnormality	1696 (19.8%)
Total reported major vital sign abnormalities	**2082 (24.3)**
Tachycardia (HR[b] > 140)	857 (10.0)
Hypotension (systolic BP[c] < 80 mmHg)	468 (5.5)
Bradycardia (HR[b] < 50)	277 (3.2)
Bradypnea (RR[d] < 10)	230 (2.7)
Hypertension (systolic BP[c] > 200 mmHg and/or diastolic BP[c] > 120 mmHg)	215 (2.5)
Hyperthermia (temp > 105° F)	35 (0.5)

[a]Percentage based on the number of cases relative to the total number of registry cases in 2021 ($N=8552$). Cases may be associated with more than one major vital sign abnormality

[b]*HR* heart rate

[c]*BP* blood pressure

[d]*RR* respiratory rate

Clinical Signs and Symptoms—Neurologic

Table 33 describes the 6409 neurologic clinical signs and symptoms reported to the Core Registry in 2021. Coma/CNS depression (24.4%), agitation (15.6%), hyperreflexia/myoclonus/clonus/tremor (12.2%), and delirium/toxic psychosis (10.5%) were the most commonly reported signs, similar to last year [4].

Table 33 Clinical signs and symptoms—neurologic

	N (%)[a]
Total unique cases with 1 + neurologic effects	4500 (52.6)
Total reported neurologic clinical effects	**6409 (74.9)**
Coma/CNS depression	2086 (24.4)
Agitation	1333 (15.6)
Hyperreflexia/myoclonus/clonus/tremor	1047 (12.2)
Delirium/toxic psychosis	899 (10.5)
Seizures	474 (5.5)
Hallucination	320 (3.7)
EPS/dystonia/rigidity	104 (1.2)
Weakness/paralysis	82 (1.0)
Numbness/paresthesia	47 (0.5)
Peripheral neuropathy (objective)	17 (0.2)

[a]Percentages based on the total number of cases reported to the registry in 2021 ($N=8552$). Cases may have reported multiple effects

Table 34 Clinical signs—cardiovascular and pulmonary

	N (%)[a]
Total unique cases with 1 + cardiovascular or pulmonary effect	1481 (17.3)
Total reported cardiovascular effects	**731 (8.5)**
Prolonged QTc (≥ 500 ms)	469 (5.5)
Prolonged QRS (≥ 120 ms)	106 (1.2)
Myocardial injury or infarction	74 (0.9)
Ventricular dysrhythmia	68 (0.8)
AV Block (> 1st degree)	14 (0.2)
Total reported pulmonary effects	**934 (10.9)**
Respiratory depression	725 (8.5)
Aspiration pneumonitis	109 (1.3)
Acute lung injury/ARDS[b]	74 (0.9)
Asthma/reactive airway disease	26 (0.3)

[a]Percentage based on number cases reporting signs or symptoms relative to total number of registry cases in 2021 ($N=8552$). Cases may be associated with more than one sign or symptom

[b]*ARDS* acute respiratory distress syndrome

Clinical Signs and Symptoms—Cardiovascular and Pulmonary

Table 34 presents the 731 cardiovascular clinical signs and 934 pulmonary clinical signs reported to the Core Registry in 2021. QTc prolongation (5.5%) and respiratory depression (8.5%) remained the most common signs in their respective categories again this year [4].

Clinical Signs—Other Organ Systems

Table 35 presents the other organ system clinical signs which include metabolic, gastrointestinal/hepatic, renal/

Table 35 Clinical signs—other organ systems

	N (%)[a]
Metabolic	
Total reported metabolic clinical effects	**710 (8.3)**[b]
Metabolic acidosis (pH < 7.2)	275 (3.2)
Elevated anion gap (> 20)	260 (3.0)
Hypoglycemia (glucose < 50 mg/dL)	112 (1.3)
Elevated osmole gap (> 20)	63 (0.7)
Gastrointestinal/hepatic	
Total reported gastrointestinal/hepatic clinical effects	**692 (8.1)**[b]
Hepatotoxicity (AST[c] ≥ 1000 IU/L)	232 (2.7)
Hepatotoxicity (ALT[d] 100–1000 IU/L)	207 (2.4)
Hepatotoxicity (ALT[d] ≥ 1000 IU/L)	133 (1.6)
Gastrointestinal bleeding	56 (0.7)
Pancreatitis	31 (0.4)
Corrosive injury	28 (0.3)
Intestinal ischemia	5 (0.1)
Renal/musculoskeletal	
Total reported renal/musculoskeletal clinical effects	**640 (7.5)**[b]
Acute kidney injury (creatinine > 2.0 mg/dL)	385 (4.5)
Rhabdomyolysis (CPK[e] > 1000 IU/L)	255 (3.0)
Hematologic	
Total reported hematologic clinical effects	**493 (5.8)**[b]
Coagulopathy (PT[f] > 15 s)	120 (1.4)
Thrombocytopenia (platelets < 100 K/μL)	114 (1.3)
Hemolysis (Hgb[g] < 10 g/dL)	111 (1.3)
Leukocytosis (WBC[h] > 20 K/μL)	109 (1.3)
Methemoglobinemia (MetHgb ≥ 2%)	25 (0.3)
Pancytopenia	14 (0.2)
Dermatologic	
Total reported dermatologic clinical effects	**225 (2.6)**[b]
Rash	128 (1.5)
Blister/Bullae	51 (0.6)
Necrosis	25 (0.3)
Angioedema	21 (0.2)

[a]Percentage based on the number of cases reporting specific clinical signs compared to the total number of registry cases in 2021 (N = 8552)

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

[c]AST aspartate aminotransferase

[d]ALT alanine transaminase

[e]CPK creatine phosphokinase

[f]PT prothrombin time

[g]Hgb hemoglobin

[h]WBC white blood cells

musculoskeletal, hematologic, and dermatologic. Metabolic abnormalities were again the most frequently reported (8.3%), and among these abnormalities, metabolic acidosis (3.2%) and an elevated anion gap (3.0%) were the most common [4]. Gastrointestinal/hepatic abnormalities were the next most commonly reported signs (8.1%), and hepatotoxicity with AST elevated above 1000 IU/L (2.7%) was the most common sign within this sub-group. Acute kidney injury (4.5%) was the most common renal/musculoskeletal abnormality. Coagulopathy (1.4%) was the most commonly reported hematological abnormality. Dermatological abnormalities were the least frequently reported abnormality (2.6%), with rash being the most common (1.5%).

Fatalities

There were 120 fatalities in 2021, comprising 1.4% of Core Registry cases and the second highest number of fatalities in the history of the ToxIC annual report. Single agent exposures were implicated in 68 cases (Table 36). Thirty-six cases involved multiple agents (Table 37), and in sixteen cases the presence of a toxicologic exposure was unknown (Table 38).

Among fatalities with known agents, there were 25 (24.0%) involving opioids: 14 single agent fatalities (20.6%) and 11 (30.6%) multiple agent fatalities. In 2021, there were 10 single agent fentanyl deaths (14.7%) compared to one single agent fentanyl death in 2020 [4]. This is the first year that fentanyl surpassed acetaminophen as the most commonly reported agent in single-agent fatalities (10 fentanyl vs 9 acetaminophen single agent fatalities) [4–7].

Acetaminophen accounted for 16 fatalities (15.4%). This represents the first year that acetaminophen did not account for the majority of single or multiple agent fatalities [4–7].

In 2021, there were 11 pediatric (age 0–18 years) deaths due to a known toxicologic exposure (10.6%), compared to 16.1% in 2020 [4]. The age range was 20 months to 18 years. Seven were single-agent exposures and four involved multiple agents. Only one pediatric death involved acetaminophen in 2021. Five deaths involved opioids in pediatric patients and four (80.0%) of these deaths involved fentanyl. One single agent ethanol death was reported in an 18-year-old.

There were 62 fatality cases in which life support was withdrawn, representing 0.7% of Core Registry cases. Brain death was declared in 26 cases.

Adverse Drug Reactions

Table 39 presents drugs commonly associated with adverse drug reactions reported to the Core Registry in 2021. A total of 253 ADRs (3.0% of cases) were reported in 2021. Lithium was again the most common drug reported (9.1%), similar

Table 36 2021 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]
21 F	Acetaminophen	QTC, CNS, AG, HPT, WBC	Yes	No	NAC
24 F	Acetaminophen	HT, TC, BC, VD, RD, CNS, MA, AG, GIB, HYS, CPT, WBC	Yes	No	Fomepizole, NAC, antiarrhythmics, vasopressors (epinephrine, norepinephrine, dopamine), hemodialysis, continuous renal replacement therapy, intubation, IV fluid resuscitation, transfusion
30 F	Acetaminophen	HT, CNS, AG, HPT, AKI	No	No	None
39 M	Acetaminophen	HT, RD, CNS, HGY, AG, OG, HPT, CPT, AKI, RBM, JD	Yes	Unknown	NAC, octreotide, vitamin K, benzodiazepines, glucose > 5%, opioids, propofol, vasopressors (norepinephrine, vasopressin), continuous renal replacement therapy, intubation, IV fluid resuscitation
42 M	Acetaminophen	HT, QRS, CNS, MA, AG, HPT, CPT, PLT, AKI	Yes	Unknown	NAC, opioids, propofol, vasopressors (norepinephrine, vasopressin), hemodialysis, continuous renal replacement therapy, intubation, IV fluid resuscitation
48 F	Acetaminophen	HT, TC, CNS, HGY, HPT, WBC, AKI	No	Unknown	Flumazenil, NAC, glucose > 5%, propofol, vasopressors (epinephrine, norepinephrine, vasopressin), continuous renal replacement therapy, intubation, IV fluid resuscitation, transfusion
58 F	Acetaminophen	HT, RD, CNS, HPT, AKI	No	No	NAC, opioids, propofol, IV fluid resuscitation
64 M	Acetaminophen	CNS, MA, RBM	Yes	Yes	NAC, vasopressors (norepinephrine, vasopressin), intubation, IV fluid resuscitation, transfusion
70 M	Acetaminophen	AG, HPT, CPT	Yes	No	NAC, vitamin K
24 M	Acetylsalicylic acid	TC, CNS, SZ, AKI	No	None	None
55 F	Amlodipine	HT, BC, RD, CNS, MA, GII, PLT	Yes	No	HIE, glucose > 5%, neuromuscular blockers, opioids, propofol, vasopressors (epinephrine, norepinephrine, vasopressin, angiotensin II), continuous renal replacement therapy, ECMO, intubation
64 M	Amlodipine	HT, BP, ALI, RD, CNS, MA, AKI	Yes	Yes	Calcium, glucagon, hydroxocobalamin, HIE, methylene blue, vasopressors (norepinephrine), intubation, IV fluid resuscitation
66 F	Amlodipine	HT, QTC, CNS, MA, HYS, AKI	Yes	Yes	Calcium, hydroxocobalamin, HIE, lipid therapy, methylene blue
34 M	Analgesic unspecified	HT, ALI, CNS, MHG	Yes	No	Methylene blue, propofol, hemodialysis, intubation
13 F	Bupropion	SZ	No	No	IV fluid resuscitation
35 M	Bupropion	QRS, QTC, RD, CNS	Yes	Yes	intubation, IV fluid resuscitation
60 M	Carbon monoxide	CNS	Yes	Unknown	HBO, intubation
33 F	Clobazam	RD, CNS, MA	Yes	Yes	vasopressors (epinephrine), intubation, IV fluid resuscitation
39 M	Cocaine	SYS, TC, QRS, AGT, CNS, DLM, MA, AG, HPT, AKI, RBM, CA	No	Yes	Calcium, fomepizole, NaHCO$_3$, insulin, glucose > 5%, CPR, ECMO, intubation, IV fluid resuscitation

Table 36 (continued)

Age / Gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
29 M	Difluoroethane	VD, QTC, RFX	No	No	Calcium, benzodiazepines, cardioversion, IV fluid resuscitation
64 M	Digoxin	HT, QRS, AG, HPT, HYS, CPT, AKI, HK, CA	Yes	No	Digoxin Fab, vasopressors (norepinephrine, vasopressin), hemodialysis, CPR, intubation, IV fluid resuscitation
72 M	Digoxin	HT, BC, VD, QRS, AVB, MI, CNS, MA, AG, AKI, CA	Yes	No	Digoxin Fab, NaHCO$_3$, antiarrhythmics, continuous renal replacement therapy, CPR
31 M	Diphenhydramine	HT, QRS, CNS, MA, AG, HPT, CPT, WBC, AKI, RBM, CA	No	No	Lipid resuscitation therapy, vasopressors (epinephrine, norepinephrine), CPR, intubation, IV fluid resuscitation
18 M	Ethanol	None	No	No	Benzodiazepines
35 F	Ethanol	HT, AP, CNS, NM, PAR, MA, GIB, HYS, CPT, AKI, JD	Yes	Yes	NAC, benzodiazepines, vasopressors (norepinephrine, vasopressin), transfusion
53 M	Ethanol	HTN, AGT, HAL	No	No	None
54 M	Ethanol	RFX, PLT	No	No	Benzodiazepines, phenobarbital, IV fluid resuscitation
88 M	Ethanol	TC, AGT, DLM, RFX	No	No	Folate, thiamine, antipsychotics, benzodiazepines, opioids, phenobarbital, IV fluid resuscitation
20 F	Fentanyl	OT, HT, BC, MI, RD, CNS, SZ, MA, HPT, CPT, RBM, CA	Yes	Unknown	NAC, naloxone/nalmefene, benzodiazepines, propofol, CPR, intubation, IV fluid resuscitation
30 F	Fentanyl	HT, MI, CNS, MA, HPT, CA	Yes	Yes	Naloxone/nalmefene, anticonvulsants, benzodiazepines, glucose > 5%, opioids, propofol, CPR, intubation, IV fluid resuscitation
36 F	Fentanyl	OT, MI, RD, CNS, AG, HPT, WBC, AKI, RBM, CA	No	No	Buprenorphine/naloxone dual formulations, naloxone OD prevention kit education or Rx, naloxone/nalmefene, antiarrhythmics, antihypertensives, beta-blockers, neuromuscular blockers, neuromuscular blockers, opioids, propofol, vasopressors (norepinephrine, dobutamine, milrinone), CPR, intubation, IV fluid resuscitation
37 M	Fentanyl	OT, HTN, HT, BP, MI, AP, CNS, MA, HPT, AKI	Yes	No	Naloxone OD prevention kit education or Rx, naloxone/nalmefene, anticonvulsants, antihypertensives, propofol, intubation, IV fluid resuscitation
37 M	Fentanyl	HT, ALI, DLM, MA, CPT, AKI	No	No	None
41 M	Fentanyl	OT, VD, CNS, MA	Yes	Unknown	None
59 M	Fentanyl	RD, CNS	No	No	Naloxone/nalmefene
20mo M	Fentanyl	HTN, TC, BP, RD, CNS, CA	Yes	Yes	Naloxone/nalmefene, anticonvulsants, benzodiazepines, dexmedetomidine, vasopressors, CPR, intubation, IV fluid resuscitation
21mo M	Fentanyl	RD, CNS	No	No	Naloxone/nalmefene, intubation, IV fluid resuscitation

Table 36 (continued)

Age / Gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
Unknown M	Fentanyl	OT, RD, CNS, CA	Yes	Yes	Naloxone/nalmefene, NaHCO₃, benzodiazepines, neuromuscular blockers, opioids, propofol, CPR, intubation, IV fluid resuscitation, therapeutic hypothermia
32 M	Heroin	OT, HT, VD, MI, ALI, RD, CNS, MA, HPT, WBC, AKI, RBM, CA	Yes	Yes	Naloxone/nalmefene, antiarrhythmics, neuromuscular blockers, propofol, vasopressors (epinephrine, norepinephrine), CPR, cardioversion, intubation, IV fluid resuscitation, therapeutic hypothermia
51 F	Heroin	OT, AP, CNS	Yes	Yes	None
62 F	Insulin	HPT, RBM	No	No	Glucose > 5%, IV fluid resuscitation
82 M	Linagliptin	HYS, RBM, SN	Yes	No	Calcium, NaHCO₃, neuromuscular blockers, opioids, intubation, IV fluid resuscitation
52 M	Lithium	AGT, CNS, AKI	Unknown		Hemodialysis, IV fluid resuscitation
56 F	Lithium	VD, DLM, RFX, CA	No		Hemodialysis, CPR, balloon pump, intubation, IV fluid resuscitation
40 F	Lorazepam	HT, TC, AP, AGT, CNS, DLM, MA, AG, OG, AKI, RBM	Yes	Unknown	Benzodiazepines, propofol, continuous renal replacement therapy, intubation, IV fluid resuscitation
16 F	Metformin	HT, MA, AG, OG, HPT, AKI	No		Vasopressors (epinephrine, norepinephrine), continuous renal replacement therapy, ECMO
80 F	Metformin	HT, HGY, AG	Yes	Yes	NaHCO₃, opioids, IV fluid resuscitation
86 M	Metformin	HT, BC, HY, QRS, QTC, RD, MA, AG, AKI, CA	No		Vasopressors (norepinephrine), hemodialysis, CPR, intubation, IV fluid resuscitation
53 F	Methamphetamine	HT, TC, HY, MI, ALI, CNS, MA, AG, HYS, CPT, PLT, WBC, AKI, RBM	Yes	No	Benzodiazepines, neuromuscular blockers, opioids, propofol, vasopressors (epinephrine, norepinephrine, vasopressin), continuous renal replacement therapy, intubation, IV fluid resuscitation, therapeutic hypothermia
68 F	Methotrexate	PAR, PCT, AKI	Unknown		Folate, urinary alkalinization, IV fluid resuscitation
52 M	Methylsalicylate	HTN, TC, RD, CNS, SZ, HPT, GIB	Yes	Unknown	Benzodiazepines, intubation, IV fluid resuscitation
76 M	Methylsalicylate	HT, VD, CNS, MA, AG, WBC, CA	No		Vasopressors (norepinephrine), urinary alkalinization, CPR, intubation, IV fluid resuscitation
30 F	Olanzapine	RD, CNS	No		Intubation, IV fluid resuscitation, magnesium
16 M	Opioid unspecified	OT, TC, ALI, RD, CNS, MA, AG, CA	Yes	No	Naloxone/nalmefene, neuromuscular blockers, vasopressors (epinephrine, norepinephrine, vasopressin), CPR, intubation, IV fluid resuscitation
70 M	Oxycodone	OT, HT, CNS	Yes	Yes	Naloxone/nalmefene
53 F	Paracetamol	HPT	Yes	No	NAC, antipsychotics, benzodiazepines, neuromuscular blockers, opioids, vasopressors (norepinephrine), hemodialysis, intubation, IV fluid resuscitation
55 M	Paraquat	AP, RD, AG, HPT, CRV, AKI, SN	No		NAC, steroids, IV fluid resuscitation

Table 36 (continued)

Age / Gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
53 M	Pyrantel	QTC, SZ	Yes	Unknown	None
21 M	Quetiapine	SHS, MI, AP, CNS, HPT, AKI, RBM, CA	Unknown	Unknown	NAC, CPR, intubation, IV fluid resuscitation
61 M	Quetiapine	SHS, CNS	No	Unknown	Intubation
63 M	Rasburicase	MHG	Yes	Unknown	Intubation, ascorbic acid
84 M	Sotalol	HT, BP, QRS, AVB, CNS	Yes	No	Glucagon, NAC, vasopressors (dopamine), IV fluid resuscitation
40 F	Unknown agent	HT, MI, AP, RD, CNS, RFX, MA, AG, HPT, CPT, CA	Yes	Yes	Calcium, NaHCO₃, anticonvulsants, benzodiazepines, opioids, propofol, vasopressors (norepinephrine, vasopressin), continuous renal replacement therapy, CPR, Intubation, IV fluid resuscitation
49 M	Unknown agent	HT, SZ, MA, AG, MHG, HYS	No	No	Methylene blue, vasopressors (epinephrine), intubation, IV fluid resuscitation, transfusion
16 Transgender	Venlafaxine		Unknown		Benzodiazepines
42 M	Verapamil	HT, BC, QTC, CNS	Yes	No	Hydroxocobalamin, HIE, lipid therapy, methylene blue, vasopressors (epinephrine, norepinephrine, phenylephrine, angiotensin II), ECMO, intubation, IV fluid resuscitation
52 F	Verapamil	HT, MI, RD, CNS, MA	Yes	No	Atropine, calcium, NaHCO₃, vasopressors (epinephrine, norepinephrine, vasopressin), intubation, IV fluid resuscitation
32 F	Warfarin	CNS, AG, GIB, HYS, CPT, CA	No	No	Factor replacement, vitamin K, CPR, intubation, IV fluid resuscitation, transfusion

[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. mo: months

[c] *AG* anion gap, *AGT* agitation, *AKI* acute kidney injury, *ALI* acute lung injury, *ARDS, AP* aspiration pneumonitis, *AVB* AV block, *BC* bradycardia, *BP* bradypnea, *CA* cardiac arrest, *CNS coma/CNS* depression, *CPT* coagulopathy, *CRV* corrosive injury, *DLM* delirium, *GIB* GI bleeding, *GII* intestinal ischemia, *HAL* hallucination, *HGY* hypoglycemia, *HK* hyperkalemia, *HPT* hepatoxicity, *HT* hypotension, *HTN* hypertension, *HYS* hemolysis, *HYT* hyperthermia, *JD* jaundice, *MA* metabolic acidosis, *MHG* Methemoglobinemia, *MI* myocardial injury/ischemia, *NM* numbness/paresthesias, *OG* osmolar gap, *OT* opioid toxidrome, *PAR* paralysis/weakness, *PCT* pancytopenia, *PLT* thrombocytopenia, *QRS* QRS prolongation, *QTC* QTc prolongation, *RBM* rhabdomyolysis, *RD* respiratory depression, *RFX* hyperreflexia/clonus/tremor, *SHS* sedative-hypnotic syndrome, *SZ* seizures, *TC* tachycardia, *VD* ventricular dysrhythmia, *WBC* leukocytosis

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; *CPR* Cardiopulmonary resuscitation, *ECMO* Extra-corporeal membrane oxygenation, *HBO* hyperbaric oxygenation, *HIE* high dose insulin euglycemic therapy, *NAC* n-Acetyl cysteine, *NaHCO₃* Sodium bicarbonate

Table 37 2021 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]
26 F	Acetaminophen, amitriptyline, fluoxetine, lamotrigine, tizanidine	AC, HT, TC, VD, QRS, QTC, RD, CNS, SZ, MA, CA	Yes	Yes	NAC, NaHCO₃, benzodiazepines, phenobarbital, vasopressors (epinephrine, norepinephrine), CPR, intubation, IV fluid resuscitation
14 F	Acetaminophen, bupropion, clonidine, sertraline	CNS	No		NAC, IV fluid resuscitation
54 F	Acetaminophen, citalopram, diphenhydramine, valproic acid	AC, HT, VD, QTC, MI, RD, CNS, DLM, RFX, SZ, MA	Yes	Unknown	NAC, antiarrhythmics, anticonvulsants, benzodiazepines, neuromuscular blockers, vasopressors (norepinephrine, vasopressin), intubation, IV fluid resuscitation
75 F	Acetaminophen, hydrocodone	HT, TC, BC, QRS, QTC, HGY, MA, AG, HPT, PNC, CPT, AKI	No		NAC, NaHCO₃, glucose > 5%, vasopressors (epinephrine, norepinephrine, vasopressin), continuous renal replacement therapy, IV fluid resuscitation
62 F	Acetaminophen, hydrocodone	OT, HT, AP, AGT, CNS, MA, AG, HPT, GIB, AKI, RBM	Yes	Yes	NAC,
52 M	Acetaminophen, ibuprofen	HTN, AKI	Unknown		NAC, antihypertensives
42 F	Acetaminophen, methadone	HT, TC, VD, QTC, ALI, CNS, MA, CPT, PLT, WBC, AKI, CA	Yes	No	NAC, antiarrhythmics, benzodiazepines, propofol, vasopressors (epinephrine, norepinephrine), CPR, intubation, IV fluid resuscitation
57 M	Acetone, diltiazem	HT, BC, RD, CNS, AKI, CA	No	No	Atropine, calcium, glucagon, HIE, vasopressors (epinephrine, norepinephrine, vasopressin, phenylephrine), CPR, intubation, IV fluid resuscitation
51 M	Amlodipine, bupropion, metoprolol	HT, BC, ALI, RD, CNS, AKI, CA	Yes	No	HIE, lipid therapy, NaHCO₃, glucose > 5%, propofol, steroids, vasopressors (epinephrine, norepinephrine), CPR, intubation, IV fluid resuscitation
62 M	Amlodipine, chlorthalidone, clonidine, hydroxyzine, pravastatin	HT, BC, CNS, CPT, AKI, RBM	No	No	Calcium, glucagon, HIE, NaHCO₃, glucose > 5%, vasopressors (norepinephrine), IV fluid resuscitation
53 M	Amlodipine, fluoxetine	HT, BC	No	No	Calcium, glucagon, HIE, naloxone/nalmefene, vasopressors (epinephrine, norepinephrine), hemodialysis
69 M	Amlodipine, meloxicam, metoprolol, opioid unspecified	HT, BC, CNS, AKI	No	No	Calcium, glucagon, HIE, lipid therapy, methylene blue, naloxone/nalmefene, NaHCO₃, vasopressors (epinephrine, norepinephrine, vasopressin, angiotensin II), continuous renal replacement therapy, intubation, IV fluid resuscitation
66 M	Amlodipine, morphine	HT, AP, RD, CNS, MA, HPT, AKI	Yes	No	Calcium, HIE, methylene blue, dexmedetomidine, opioids, propofol, intubation, IV fluid resuscitation

Table 37 (continued)

Age / Gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
53 M	Bupropion, ethanol, lacosamide, midodrine, olanzapine	HT, TC, VD, QRS, QTC, RD, CNS, SZ, MA, HPT, HYS, PLT, WBC, AKI	Yes	Unknown	Atropine, folate, NaHCO$_3$, thiamine, antiarrhythmics, benzodiazepines, neuromuscular blockers, phenobarbital, propofol, vasopressors (epinephrine, norepinephrine), intubation, IV ffluid resuscitation
16 M	Caffeine, methamphetamine	TC, MI, CNS, RFX, SZ, HGY, HPT, CPT, PLT, WBC, AKI	Unknown		NAC, octreotide, vitamin K, anticonvulsants, benzodiazepines, glucose>5%, neuromuscular blockers, opioids, intubation
Unknown M	Cannabinoid (nonsynthetic), cocaine, heroin, methamphetamine	AGT, DLM, HAL	No		Antipsychotics, benzodiazepines, dexmedetomidine, ketamine, neuromuscular blockers, opioids, propofol, intubation, IV fluid resuscitation
36 M	Cannabinoid (nonsynthetic), methamphetamine	SYL, HT, TC, RD, CNS, PLT, AKI	No		Folate, thiamine, vasopressors (norepinephrine, neosynephrine), intubation, IV fluid resuscitation
75 M	Carvedilol, hydralazine	HT, BC, CNS, AKI, CA	No		vasopressors (norepinephrine, dopamine), CPR, intubation, IV fluid resuscitation, pacemaker
44 F	Clonidine, verapamil	HT, BC, VD, QRS, QTC, AVB, MI, ALI, CNS, MA, AG, HPT, WBC, AKI, CA	No		Calcium, HIE, NaHCO$_3$, vasopressors (epinephrine, norepinephrine, vasopressin, dopamine, dobutamine), continuous renal replacement therapy, CPR, intubation, IV fluid resuscitation, pacemaker
31 M	Cocaine, fentanyl	OT, HT, BP, QTC, RD, CNS, MA, HPT, AKI, CA	Yes	Unknown	NaHCO$_3$, antiarrhythmics, vasopressors (norepinephrine, vasopressin), intubation, IV fluid resuscitation
41 M	Cocaine, methamphetamine, yohimbine	HTN, HT, TC, VD, QTC, AP, CNS, MA, CA	Yes	Yes	Calcium, bronchodilators, opioids, vasopressors (epinephrine, norepinephrine, vasopressin), CPR, intubation, IV fluid resuscitation, therapeutic hypothermia
51 M	Cyclobenzaprine, diltiazem, insulin, sertraline	SHS, HT, TC, RD, CNS, HGY, AKI	Yes	Yes	Calcium, octreotide, glucose > 5%, vasopressors (norepinephrine), activated charcoal, intubation, IV fluid resuscitation
46 M	Delta-9-tetrahydrocannabinol, methamphetamine, phencyclidine	SYS, HTN, VD, TC, MI, RD, CNS, MA, RBM, CA	Yes	No	Antipsychotics, benzodiazepines, propofol, vasopressors (norepinephrine), CPR, cardioversion, intubation, IV fluid resuscitation, therapeutic hypothermia
53 M	Diltiazem, propafenone	HT, BC, VD, QRS, CNS, MA, AG, HPT, PNC, GII, AKI	No		Calcium, HIE, lipid therapy, methylene blue, vasopressors (epinephrine, norepinephrine), continuous renal replacement therapy, ECMO, IV fluid resuscitation, pacemaker

Table 37 (continued)

Age / Gender[b]	Agents involved	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment[d]
15 M	Ethanol, fentanyl	OT, SHS, RD, CNS, MA, HPT, AKI, CA	Yes	Yes	Vasopressors (epinephrine, norepinephrine, vasopressin, phenylephrine), CPR, intubation
37 F	Ethanol, unknown agent	RD, CNS	No		Antipsychotics, benzodiazepines, neuromuscular blockers, propofol, intubation, IV fluid resuscitation
50 F	Ethanol, unknown agent	HT, QTC, RD, CNS, DLM, HAL, MA, AG, HPT, GII, HYS, CPT, PLT, WBC, AKI, RBM	No		Folate, fomepizole, NAC, thiamine, dexmedetomidine, neuromuscular blockers, opioids, phenobarbital, propofol, vasopressors (epinephrine, norepinephrine, vasopressin, phenylephrine), continuous renal replacement therapy, intubation, IV fluid resuscitation
2 F	Fentanyl, morphine	OT, HT, BC, BP, CNS, MA, CA	No		Naloxone/nalmefene, CPR
30 M	Gabapentin, lacosamide	RFX	No		Benzodiazepines
77 F	Haloperidol, olanzapine, quetiapine	NMS, HYT, VD, MI, RD, AGT, CNS, DLM, HAL, RFX, AKI, RBM	No		Bromocriptine, dantrolene, benzodiazepines, neuromuscular blockers, propofol, vasopressors (norepinephrine), continuous renal replacement therapy, intubation, IV fluid resuscitation
86 M	Heroin, oxycodone	OT, MI, RD, CNS, AKI	Yes	No	Naloxone/nalmefene, benzodiazepines, IV fluid resuscitation
57 M	Ketamine, lacosamide, levetiracetam, midazolam, phenytoin, propofol, valproic acid	VD, QRS	No		NaHCO₃, vasopressors (epinephrine, vasopressin), intubation
16 M	Marijuana, methadone	HT, AP, AGT, CNS, MA, AKI, RBM	Yes	No	Anticonvulsants, opioids, propofol, vasopressors (epinephrine), intubation, IV fluid resuscitation
70 F	Metoprolol, nifedipine	HT, BC, AVB, RD, CNS, MA, AG, AKI	Yes	Unknown	Calcium, glucagon, NaHCO₃, benzodiazepines, vasopressors (norepinephrine, vasopressin, phenylephrine, dobutamine), intubation, IV fluid resuscitation
30 M	Olanzapine, rizatriptan	AC, TC, RD, CNS, RFX	No		Naloxone/nalmefene, intubation, IV fluid resuscitation
52 M	Venlafaxine, unknown agent	SHS, HT, VD, RD, CNS, HPT, RBM	No		NAC, naloxone/nalmefene

[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

[c] *AC* anticholinergic, *AG* anion gap, *AGT* agitation, *AKI* acute kidney injury, *ALI* acute lung injury/ARDS, *AP* aspiration pneumonitis, *AVB* AV block, *BC* bradycardia, *BP* bradypnea, *CA* cardiac arrest, *CNS* coma/CNS depression, *CPT* coagulopathy, *DLM* delirium, *GII* bleeding, *GII* intestinal ischemia, *HAL* hallucination, *HPT* hepatoxicity, *HTN* hypotension, *HYS* hemolysis, *HYT* hyperthermia, *MA* metabolic acidosis, *MI* myocardial injury/ischemia, *NMS* neuroleptic malignant syndrome, *OT* opioid toxidrome, *PLT* thrombocytopenia, *PNC* pancreatitis, *QRS* QRS prolongation, *QTC* QTc prolongation, *RBM* rhabdomyolysis, *RD* respiratory depression, *RFX* hyperreflexia/clonus/tremor, *SHS* sedative-hypnotic syndrome, *SYL* sympatholytic syndrome, *SYS* sympathomimetic syndrome, *SZ* seizures, *TC* tachycardia, *VD* ventricular dysrhythmia, *WBC* leukocytosis

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; *CPR* Cardiopulmonary resuscitation, *ECMO* Extra-corporeal membrane oxygenation, *HIE* high dose insulin euglycemic therapy, *NAC* n-Acetyl cysteine, *NaHCO₃* Sodium bicarbonate

Table 38 2021 Fatalities reported in ToxIC Registry with unknown toxicological exposure[a]

Age / Gender[b]	Clinical findings[c]	Life support withdrawn	Brain death confirmed	Treatment reported[d]
13 F	HT, TC, VD, CNS, SZ, MA, WBC, AKI	No		Flumazenil, lipid therapy, naloxone/nalmefene, antiarrhythmics, vasopressors (epinephrine), intubation, IV fluid resuscitation
16 M	CNS, RFX, SZ, RBM	Yes	Yes	Benzodiazepines, intubation
17 M	HT, RD, CNS, AG	Yes	Yes	None
19 M	HT, QTC, MI, AP, RD, CNS, MA	Yes	Yes	Flumazenil, vasopressors (norepinephrine), intubation
20 M	HT, CNS, MA, CA	Yes	Yes	Naloxone/nalmefene, CPR
24 F	HT, TC, VD, MI, ALI, AGT, MA, AG, HPT, AKI, RBM	Yes	Yes	None
30 M	RD, CNS, MA, AG	Yes	Yes	None
40 M	None	No		None
43 F	CNS, MA	Yes	Unknown	NaHCO$_3$, vasopressors (norepinephrine), intubation, IV fluid resuscitation
46 F	AGT, DLM	Yes	Yes	None
49 M	None	Unknown		Methadone, opioids, steroids
61 F	SS, HTN, HYT, RD, RFX, MHG	Unknown		Opioids, intubation, IV fluid resuscitation
69 F	RD, DLM, PAR, AKI	No		None
78 F	HT, BC, RD, CNS	Yes	No	Vasopressors (norepinephrine), IV fluid resuscitation
Unknown M	AK, SHS, HT, TC, BP, QRS, QTC, RD, CNS, MA, HPT, CPT, PLT, CA	No		Folate, fomepizole, NAC, pyridoxine, NaHCO$_3$, thiamine, vasopressors (epinephrine, norepinephrine, vasopressin, dobutamine, phenylephrine, angiotensin II), CPR, ECMO, intubation, IV fluid resuscitation
Unknown M	HT, TC, BC, BP, MI, AP, CNS, MA, GIB, HYS, CPT, PLT, WBC, AKI, RBM	No		None

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals No or Unknown

[b] Age in years unless otherwise stated

[c] *AG* anion gap, *AGT* agitation, *AK* alcoholic ketoacidosis, *AKI* acute kidney injury, *ALI* acute lung injury/ARDS, *AP* aspiration pneumonitis, *BC* bradycardia, *BP* bradypnea, *CA* cardiac arrest, *CNS* coma/CNS depression, *CPT* coagulopathy, *DLM* delirium, *GIB* GI bleeding, *HPT* hepatoxicity, *HT* hypotension, *HTN* hypertension, *HYS* hemolysis, *HYT* hyperthermia, *MA* metabolic acidosis, *MHG* Methemoglobinemia, *MI* myocardial injury/ischemia, *PAR* paralysis/weakness, *PLT* thrombocytopenia, *QRS* QRS prolongation, *QTC* QTc prolongation, *RBM* rhabdomyolysis, *RD* respiratory depression, *RFX* hyperreflexia/clonus/tremor, *SHS* sedative-hypnotic syndrome, *SS* serotonin syndrome, *SZ* seizures, *TC* tachycardia, *VD* ventricular dysrhythmia, *WBC* leukocytosis

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; *CPR* Cardiopulmonary resuscitation, *ECMO* Extracorporeal membrane oxygenation, *NAC* n-Acetyl cysteine, *NaHCO$_3$* Sodium bicarbonate

to previous years [4–7]. One of the most common reported adverse drug reactions was bradycardia during remdesivir treatment.

Treatment

Antidotal Therapy

Table 40 describes the 4043 antidotes reported to the Core Registry in 2021. Similar to last year, N-acetylcysteine (24.8%) was the most common antidote reported [4]. This year, thiamine (20.6%) and folate (18.8%) were increasingly reported. Naloxone/nalmefene comprised 12.8% of antidotes reported, compared to 15.5% in 2020. In 2021, 47.3% of Core Registry cases received at least one antidote, compared to 31.0% in 2020 [4].

Antivenom Therapy

Table 41 presents data on antivenom therapies reported in 2021. Crotalidae polyvalent immune Fab (ovine) made up the majority (52.7%) of antivenom administered. Crotalidae immune Fab2 (equine) antivenom, introduced in 2019 (19.9%), increased to 35.3% of cases of administered

Table 39 Most common drugs associated with adverse drug reactions

	N (%)
Lithium	23 (9.1)
Haloperidol	13 (5.1)
Metformin	11 (4.3)
Digoxin	10 (4.0)
Sertraline	8 (3.2)
Dapsone	8 (3.2)
Quetiapine	7 (2.8)
Risperidone	7 (2.8)
Olanzapine	6 (2.4)
Bupropion	6 (2.4)
Aripiprazole	5 (2.0)
Glipizide	5 (2.0)
Insulin	5 (2.0)
Miscellaneous[a]	139 (54.9)
Class total	**253 (100)**

[a]Includes gabapentin, clonidine, methotrexate, acetaminophen, baclofen, tramadol, valproic acid, fentanyl, ziprasidone, metoprolol, hydroxyzine, benztropine, phenytoin, fluphenazine, ethanol, diphenhydramine, lorazepam, heroin, fluoxetine, nadolol, diltiazem, cocaine, tizanidine, trazodone, propranolol, carbamazepine, oxycodone, oxcarbazepine, cannabidiol, buprenorphine, cefepime, arginine, fluconazole, flecainide, carvedilol, cefdinir, cariprazine, cyclobenzaprine, enalapril, cytarabine (cytosine arabinoside), duloxetine, chloral hydrate, clomipramine, clonazepam, clozapine, diazepam, dextromethorphan, delta-9-tetrahydrocannabinol, cyclophosphamide, escitalopram, trifluoperazine, linezolid, pelabresib, phenobarbital, pregabalin, prochlorperazine, rasburicase, sotalol, paliperidone, topiramate, oxybutynin, trihexyphenidyl, trimeresurus unspecified (pit viper unspecified), venlafaxine, verapamil, vitamin c (ascorbic acid), warfarin, zinc, sulfonylurea unspecified, methylene blue, ifosfamide, lacosamide, lamotrigine, lidocaine, lisdexamfetamine, zolpidem, loxapine, paroxetine, methadone, guanfacine, methylphenidate, metoclopramide, mirtazapine, morphine, naloxone, nitroprusside, nitrous oxide, and meperidine

Table 40 Antidotal therapy

	N (%)[a]
N-Acetylcysteine	1002 (24.8)
Thiamine	834 (20.6)
Folate	759 (18.8)
Naloxone/nalmefene	517 (12.8)
Sodium bicarbonate	240 (5.9)
Fomepizole	114 (2.8)
Calcium	107 (2.6)
Physostigmine	64 (1.6)
Glucagon	62 (1.5)
Atropine	39 (1.0)
Insulin-euglycemic therapy	39 (1.0)
Octreotide	30 (0.7)
Carnitine	26 (0.6)
Flumazenil	25 (0.6)
Methylene blue	25 (0.6)
Lipid resuscitation therapy	24 (0.6)
Phenobarbital	24 (0.6)
Vitamin K	24 (0.6)
Cyproheptadine	23 (0.6)
Pyridoxine	21 (0.5)
Fab for digoxin	11 (0.3)
Hydroxocobalamin	11 (0.3)
Botulinum antitoxin	6 (0.1)
Bromocriptine	4 (0.1)
Dantrolene	3 (0.1)
Anticoagulation reversal	2 (<0.1)
Factor replacement	2 (<0.1)
Ethanol	1 (<0.1)
2-PAM	1 (<0.1)
Uridine triacetate	1 (<0.1)
Total	**4043 (100)**

[a]Percentages based on the total number of antidotes administered (N=4043); 2856 (70.6%) cases received at least one antidote. Cases may have involved the use of multiple antidotes

Table 41 Antivenom therapy

	N (%)[a]
Crotalidae polyvalent immune fab (ovine)	109 (52.7)
Crotalidae immune fab$_2$ (equine)	73 (35.3)
Other snake antivenom	22 (10.6)
Scorpion antivenom	2 (1.0)
Spider antivenom	1 (0.5)
Total	**207 (100)**

[a]Percentages based on the total number of antivenom treatments administered (N=207)

Table 42 Supportive care—pharmacologic

	N (%)[a]
Benzodiazepines	2024 (40.9)
Phenobarbital	576 (11.6)
Opioids	531 (10.7)
Propofol	372 (7.5)
Vasopressors	287 (5.8)
Antipsychotics	279 (5.6)
Neuromuscular blockers	181 (3.7)
Dexmedetomidine	146 (3.0)
Glucose > 5%	121 (2.4)
Anticonvulsants	91 (1.8)
Antihypertensives	73 (1.5)
Ketamine	70 (1.4)
Beta-blockers	61 (1.2)
Albuterol and other bronchodilators	60 (1.2)
Steroids	46 (0.9)
Antiarrhythmics	23 (0.5)
Vasodilators	4 (0.1)
Total	**4945 (100)**

[a]Percentages based on the total number of pharmacologic interventions (N=4945); 3079 registry cases (36.0%) received at least one pharmacologic intervention. Cases may have involved the use of multiple interventions

Table 43 Supportive care—nonpharmacologic

	N (%)[a]
IV fluid resuscitation	3540 (78.8)
Intubation/ventilatory management	789 (17.6)
CPR[b]	66 (1.5)
Transfusion	41 (0.9)
ECMO[c]	15 (0.3)
Therapeutic hypothermia	12 (0.3)
Pacemaker	11 (0.2)
Cardioversion	10 (0.2)
Hyperbaric oxygen	9 (0.2)
Transplant	1 (<0.1)
Balloon pump	1 (<0.1)
Total	**4495 (100)**

[a]Percentages based on the total number of treatments administered (N=4495); 3769 registry cases (42.6%) received at least one form of nonpharmacologic treatment. Cases may have involved the use of multiple forms of treatment

[b]CPR cardiopulmonary resuscitation

[c]ECMO extracorporeal membrane oxygenation

antivenom in 2021. This continues to represent an upward trend (31.0% of cases in 2020) [4].

Table 44 Chelation therapy

	N (%)[a]
DMSA[b]	10 (55.6)
BAL[c]	3 (16.7)
EDTA[d]	3 (16.7)
Deferoxamine	2 (11.1)
Total	**18 (100)**

[a]Percentages based on the total number of chelation treatments administered (18); 15 registry cases received at least one form of chelation treatment

[b]DMSA dimercaptosuccinic acid

[c]BAL British anti-Lewisite (dimercaprol)

[d]EDTA ethylenediamine-tetraacetic acid

Table 45 Supportive care—decontamination

	N (%)[a]
Activated charcoal	284 (81.8)
Whole-bowel irrigation	27 (7.8)
Gastric lavage	24 (6.9)
Irrigation	12 (3.5)
Total	**347 (100)**

[a]Percentages based on the total number of decontamination interventions (N=347); 322 registry cases (3.8%) received at least one decontamination intervention. Cases may have involved the use of multiple interventions

Pharmacologic Supportive Care

Table 42 describes the 4945 pharmacologic supportive care treatments reported in 2021. Benzodiazepines were the most commonly reported agents (40.9%), followed by phenobarbital (11.6%) and opioids (10.7%) [4–7].

Non-pharmacologic Supportive Care

Table 43 presents non-pharmacologic supportive care treatments reported to the Core Registry in 2021. Intravenous fluid resuscitation (78.8%) and intubation/ventilatory management (17.6%) remain the most common treatments in this category, similar to previous years [4–7].

Chelation Therapy

Table 44 presents data on chelation therapy administration. There were 18 chelation agents reported in 2021. DMSA was the most common chelator administered (55.6%).

Table 46 Enhanced elimination

	N (%)^a
Hemodialysis (other indication)	49 (25.1)
Urinary alkalinization	47 (24.1)
Continuous renal replacement therapy	45 (23.1)
Hemodialysis (toxin removal)	44 (22.6)
Multiple-dose activation charcoal	10 (5.1)
Total	**195 (100)**

^{a}Percentages based on the total number of treatments administered ($N = 195$); 171 registry cases (2.0%) received at least one form of enhanced elimination

Supportive Care—Decontamination Interventions

Table 45 describes the 347 decontamination interventions administered. Activated charcoal again represented the majority of interventions (81.8%) in this class [4–7]. Whole-bowel irrigation represented 7.8% of decontamination interventions.

Enhanced Elimination Interventions

Table 46 presents the enhanced elimination interventions reported. Hemodialysis for other reasons (25.1%), urinary alkalinization (24.1%), followed by continuous renal replacement therapy (23.1%) and hemodialysis for toxin removal (22.6%) were the most commonly reported interventions in this class.

Discussion

This report describes the twelfth year of data collected for the ToxIC Core Registry. Core Registry case numbers increased this year, following a decrease in 2020 case numbers due to the COVID-19 pandemic. The Core Registry also continued to grow, adding five new sites this year.

The Core Registry represents a wide geographic distribution of cases evaluated by medical toxicologists and can be used synergistically with other national registries, including the National Poison Data System, to evaluate poisoning trends, identify novel exposures, explore relationships with concomitant public health crises, and assess their public health implications.

This 12th ToxIC annual report finds overall 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 Core Registry are discussed below.

The opioid class continued as the second most common agent class reported to the Core Registry this year. The agent

class incidence gap between opioid and non-opioid analgesics also narrowed from 2.8% in 2020 to 1.8% in 2021 [4].

This is the first year that fentanyl is the predominant opioid sub-class reported to the Core Registry. Previously, in 2020 and 2019, heroin had been the primary opioid sub-class reported in ToxIC [4, 5]. In 2021, among patients with opioid exposures reported in the registry, there was significantly increased odds of fentanyl exposure [OR 1.97, 95% CI 1.67–2.33], and significantly decreased odds of heroin exposure [OR 0.55, 95% CI 0.46–0.66] compared to 2020. This finding likely reflects the growing trend of rising synthetic opioid prevalence, including fentanyl, across the United States [8]. Additionally, this finding may reflect increased fentanyl laboratory testing across ToxIC sites.

In 2021, ethanol became the third most common agent class (10.7%) reported, narrowly overtaking the antidepressant class (10.5%). It has been increasing in incidence over the last few years: it represented only 7.2% of reported cases in 2019 and 8.4% of cases in 2020 [4, 5].

Marijuana and THC/CBD-related products continue to represent the majority of the psychoactive class. This year, the relative contribution of delta-9-tetrahydrocannabinol skyrocketed from only 6.9% in 2020 to 17.8% in 2021. The relative contribution of synthetic cannabinoid cases continued to fall, comprising only 5.0% of cases this year.

Interestingly, kratom was increasingly reported to the Core Registry this year compared to previous years [4, 5]. While kratom reports had previously comprised approximately 16% of plant/fungi exposures, this year, kratom was the most commonly reported plant/fungi exposure at 32.6%.

Regarding envenomations, the incidence of Crotalus and Agkistrodon envenomations were slightly decreased this year, but one species did not predominate the class. In addition, the use of Crotalidae immune Fab2 (equine) antivenom continued to increase again this year (35.3% in 2021 vs. 31.0% in 2020) [4].

Fatalities

This year, there were a record number of fatalities entered into the Core Registry (120 total fatalities), although the difference was not statistically significant compared to 2020 [OR 1.16, 95% CI 0.87–1.54]. In previous years, acetaminophen contributed to the largest burden of fatalities in both single agent and multiple agent categories. This is the first year that opioids account for the largest burden of fatalities, and the number of opioid-associated fatalities has doubled in one year [4]. These trends are reflective of the ongoing opioid epidemic across the United States.

Five single agent deaths were also attributed to ethanol alone, which represents an increase from previous years [4, 5]. One adult male died after carbon monoxide exposure.

The total number of pediatric deaths due to a toxicologic exposure continued to decrease from 2020 to 2021. However, a larger burden of pediatric deaths was attributed to opioids, nearly doubling in a single year (five deaths in 2021, three deaths in 2020) [4, 5]. Two children under age 24 months died following fentanyl exposures.

New Demographics—Marital, Military, and Housing Status

This year, the registry worked to collect enhanced demographic data to better evaluate and understand poisonings among specific patient sub-populations. Among those with available data, general trends showed that patients entered into the registry were single (70.1%), had no prior military service (98.0%), and had secure housing (93.4%). Future efforts will focus on consistently capturing these data elements in registry entries.

ToxIC Novel Opioid and Stimulant Exposures

In 2021, 117 cases were submitted to the ToxIC NOSE project from 18 sites in the United States. Interesting exposures reported from NOSE cases highlighted opioids in breastmilk, fentanyl adulterants, buprenorphine toxicity in pediatric patients, and phencyclidine analogs.

COVID-19

The ToxIC Registry continued to collect COVID-19 specific data throughout 2021 utilizing the set of COVID-19-specific questions incorporated into the Core Registry in August 2020. These questions collected data on a patient's COVID-19 status and if the toxicologic exposure was related to the patient's COVID-19 status.

As expected, more patients entered into the registry in 2021 were COVID-19 positive (2.1% in 2021 vs 1.6% in 2020). The toxic exposures in COVID-19-positive patients were largely related to analgesic use (21.9% opioid analgesics, 19.7% non-opioid analgesics). Of the COVID-19-positive patients presenting with a toxic exposure, the five most common reasons for encounter include intentional pharmaceutical (41.6%), withdrawal of ethanol (12.4%), a malicious/criminal exposure event (11.2%), interpretation of toxicological lab data (7.9%), and occupational evaluation (6.7%).

Medical toxicologists noted that 92 (1.1%) of registry patients had an exposure related to their COVID-19 status. The distribution of agent classes in this sub-population was similar to overall agent class trends; the predominant agent classes included non-opioid analgesics (19.6%), opioids (18.4%), and ethanol (16.3%). Future efforts may aim to further understand reasons for the toxicologic exposure being related to COVID-19 status (treatment, prophylaxis, etc.) to further explore relationships between concomitant public health crises.

Limitations

The ToxIC Core Registry is a unique prospective database of cases in which bedside or telemedicine consultation is performed by medical toxicologists, enabling an informed relationship between exposures and clinical outcomes; however, limitations to the Core Registry do exist. One possible limitation is a bias towards inclusion of more severe case presentations, as cases are only included if they undergo sub-specialty 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 Core Registry likely represents a different population from other data sources, such as those maintained by Poison Centers. Regional differences may lead to a disproportionate number of specific cases reported based on variations in drug use, misuse, and other toxic exposures. The ToxIC Core Registry includes sites from multiple diverse locations, but the entire country is not uniformly represented. Larger academic medical centers with greater numbers of medical toxicology faculty may be over-represented in the registry.

At the level of the individual sites, there may be a reporting bias towards more complicated or interesting cases. Although the Core Registry's principal goal, 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; this limitation is likely most significant with regard to illicit drug exposure, about which patients may be hesitant to disclose detailed information. Additionally, demographic information may be misclassified by toxicologists when patients are unconscious or unable to self-identify gender, race, or ethnicity. Lastly, efforts are made to continually improve the quality of data collected. While member sites are instructed to complete all applicable data fields, there are still cases and data fields with incomplete information. This remains an issue for collection of race and ethnicity data, for example. Efforts continue to support quality data collection and follow up on missing data where applicable.

Conclusions

The ToxIC project continues to grow and evolve, including the Core Registry and additional surveillance projects. The Core Registry remains unique among databases in that it represents prospective data collected from cases evaluated by medical toxicologist specialists. 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. The registry's prospective nature also allows research efforts examining changes in toxicology trends during concomitant public health crises. Continued quality improvement and surveillance efforts remain areas of focus for the Core Registry and ToxIC.

Declarations

Conflict of Interest JSL, DLK, MBS, LAF, AMK, SLC, SL, PMW, JB, KA: These authors have no conflicts of interest to report.
HN: The work and thoughts herein are those of the author (HN) and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

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