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class, clinical signs and symptoms, treatments and antidotes administered, mortality, and whether life support was withdrawn.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

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                                                |
|                  | Houston           | William P. Clements Jr University Hospital                                |
| Canada           | Calgary           | HCA Houston Healthcare Kingwood                                            |
|                  |                   | Foothills Medical Centre                                                  |
|                  |                   | Peter Lougheed Centre                                                     |
| England          | London*           | Guy's and St Thomas' NHS Foundation Trust*                                |
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 8,552 cases entered into the registry in 2021, 7,884 included at least one specific agent of exposure. Single agents were involved in 5,541 cases. Consistent with previous years, the non-opioid analgesic class was the most common class of drugs reported (14.9%), but the proportion...
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.
Sedative Hypnotics

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

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Table 6 Reason for medical toxicology encounter

| Reason for Intentional Exposure | N (%) |
|---------------------------------|-------|
| 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) |
| Alcohol 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) |

*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

| Reason for Intentional Pharmaceutical Exposure Subgroup | N (%) |
|-------------------------------------------------------|-------|
| Attempt at self-harm | 3009 (76.0) |
| Misuse/abuse | 415 (10.5) |
| Therapeutic use | 294 (7.4) |
| Unknown | 240 (6.1) |
| Total | 3958 (100) |

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

*Attempt at self-harm—suicidal intent sub-classification

| Reason for Intent to Harm | N (%) |
|---------------------------|-------|
| Suicidal intent | 2668 (88.7) |
| Suicidal intent unknown | 239 (7.9) |
| No suicidal intent | 102 (3.4) |
| Total | 3009 (100) |

*Percentage based on number of cases indicating attempt at self-harm

Table 8 New demographic variables

| Marital Status | N (%) |
|----------------|-------|
| Total reported marital status | 4945 (57.8) |
| Married | 994 (20.1) |
| Divorced | 419 (8.5) |
| Single | 3468 (70.1) |
| Widowed | 64 (1.3) |
| Total | 4945 (100) |

*Percentage based on reported cases (N=4945)

| Military Service | N (%) |
|------------------|-------|
| Total reported military status | 3967 (46.4) |
| Yes, previous military service | 78 (2.0) |
| No previous military service | 3889 (98.0) |
| Total | 3967 (100) |

*Percentage based on reported cases (N=3967)

| Housing Status | N (%) |
|----------------|-------|
| Total reported housing status | 6311 (73.8) |
| Secured housing | 5894 (93.4) |
| Undomiciled | 365 (5.8) |
| Other | 52 (0.8) |
| Total | 6311 (100) |

*Percentage based on reported cases (N=6311)

Table 9 Addiction medicine consultations

| Addiction Medicine Consultation | 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) |

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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 (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
(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 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) |
| Herbasls | 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) |

| 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) |
| Herbasls | 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) |

| 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) |
| Miscellaneousa | 14 (0.8) |
| Class total | 1753 (100) |

*aPercentages based on total number of reported agent entries from COVID-19-positive patients (N=178).

*bIncludes analgesic unspecified, indomethacin, ketorolac, mefenamic acid, metamizole (dipyrone), nabumetone, non-steroidal anti-inflammatory drug (NSAID) unspecified, piroxicam, and salsalate.
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

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| 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)    |
| Miscellaneousa | 22 (1.4) |
| **Class total** | **1546 (100)** |

*aIncludes acetyl fentanyl, buprenorphine (AP 237, 1-butyryl-4-cinnamylpiperazine), depropionylfentanyl, dihyrocodeine, diphenoxylate, fluorofentanyl, hydromorphone, loperamide, meperidine, methylfentanyl (3- or alpha), N-piperidinyl etonitazene, oxymorphone, and tapentadol

| 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)  |
| Miscellaneousa | 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)   |
| Miscellaneousb | 7 (0.6) |
| **Class total** | **1239 (100)** |

*aIncludes vortioxetine, agametamine, mianserin
*bIncludes 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.
Household Products

Table 29 describes household products reported to the Core Registry. Cleaning solutions and disinfectants (23.3%) and sodium hypochlorite ≤ 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%).
### 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%).
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.

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

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

| 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)    |

^aPercentages based on the total number of cases reported to the registry in 2021 (N=8552). Cases may have reported multiple effects

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].

Table 34  Clinical signs—cardiovascular and pulmonary

| 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 dysrhythm                       | 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)  |

^aPercentages 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

^bARDS 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/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<sup>a</sup>: Single Agent

| Age / Gender<sup>b</sup> | Agents involved       | Clinical findings<sup>c</sup>                                                                 | Life support withdrawn | Brain death confirmed | Treatment<sup>d</sup>                                                                 |
|-------------------------|-----------------------|----------------------------------------------------------------------------------------------|------------------------|-----------------------|---------------------------------------------------------------------------------------|
| 21 F                    | Acetaminophen         | QTC, CNS, AG, HPT, WBC                                                                      | Yes                    | No                    | NAC, Fomepizole, NAC, antiarrhythmics, vasopressors (epinephrine, norepinephrine, dopamine), hemodialysis, continuous renal replacement therapy, intubation, IV fluid resuscitation, transfusion |
| 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                     | No                    | Flumazenil, NAC, glucose > 5%, propofol, vasopressors (epinephrine, norepinephrine, vasopressin), continuous renal replacement therapy, intubation, IV fluid resuscitation |
| 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                     | No                    | 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                     | No                    | Calcium, fomepizole, NaHCO₃, insulin, glucose > 5%, CPR, ECMO, intubation, IV fluid resuscitation |
| Age / Gender | Agents involved | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment |
|--------------|----------------|------------------|-----------------------|----------------------|-----------|
| 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, NaHCO₃, 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 |
| 88 M         | Ethanol         | RFX, PLT         | No                    | No                   | Benzodiazepines, 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                   | Naloxone OD prevention kit education or Rx, naloxone/nalmefene, antagonists, anticonvulsants, 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                   | Unknown              | None |
| 41 M         | Fentanyl        | OT, VD, CNS, MA  | Yes                  | Unknown              | None |
| 59 M         | Fentanyl        | RD, CNS          | | 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                   | Naloxone/nalmefene, intubation, IV fluid resuscitation |
| Age / Gender | Agents involved | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment |
|--------------|----------------|------------------|------------------------|-----------------------|-----------|
| Unknown M    | Fentanyl       | OT, RD, CNS, CA  | Yes                    | Yes                   | Naloxone/nalmefene, NaHCO₃, 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                     |                       | 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 alkalization, 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 alkalization, 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         | Oxycodeone     | 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 | Agents involved | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment |
|--------------|----------------|-------------------|------------------------|-----------------------|-----------|
| 53 M Pyrantel | QTC, SZ        | Yes               | Unknown                | None                  |
| 21 M Quetiapine | SHS, MI, AP, CNS, HPT, AKI, RBM, CA | Unknown | NAC, CPR, intubation, IV fluid resuscitation |
| 61 M Quetiapine | SHS, CNS       | No                | Unknown                | Intubation            |
| 63 M Rasburicase | MHG          | Yes               | Unknown                | Glucagon, NAC, vasopressors (dopamine), IV fluid resuscitation |
| 84 M Sotalol | HT, BP, QRS, AVB, CNS | Yes             | No                     | Calcium, NaHCO₃, anticonvulsants, benzodiazepines, opioids, propofol, vasopressors (norepinephrine, vasopressin), continuous renal replacement therapy, CPR, Intubation, 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                | Methylen blue, vasopressors (epinephrine), intubation, IV fluid resuscitation, transfusion |
| 16 Transgender Venlafaxine | HT, BC, QTC, CNS | Unknown | Benzodiazepines |
| 42 M Verapamil | HT, BC, QTC, CNS | Yes             | No                     | Hydroxocobalamine, 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                | 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, GI intestinal ischemia, HAL hallucination, HGY hypoglycemia, HK hyperkalemia, HPT hepatotoxicity, 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 toxicity, 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, SN dernal necrosis, 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, 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: Multiple Agents

| Age / Gender | Agents involved | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment |
|--------------|-----------------|-------------------|------------------------|-----------------------|-----------|
| 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 | | 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 | | Calcium, glucagon, HIE, NaHCO₃, glucose > 5%, vasopressors (norepinephrine), IV fluid resuscitation |
| 53 M         | Amlodipine, fluoxetine | HT, BC | No | | Calcium, glucagon, HIE, naloxone/nalmefene, vasopressors (epinephrine, norepinephrine), hemodialysis |
| 69 M         | Amlodipine, melexicam, metoprolol, opioid unspecified | HT, BC, CNS, AKI | 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 |
| Age / Gender | Agents involved | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment |
|--------------|-----------------|-------------------|------------------------|-----------------------|-----------|
| 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, NaHCO₃, thiamine, antiarrhythmics, benzodiazepines, neuromuscular blockers, phenobarbital, propofol, vasopressors (epinephrine, norepinephrine), intubation, IV fluid 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 | Antiarrhythmics, 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, vasoppressors (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, NaHCO₃, 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 | NaHCO₃, 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-tetrahydrocannabino, 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 |
| Age / Gender<sup>b</sup> | Agents involved | Clinical findings<sup>c</sup> | Life support withdrawn | Brain death confirmed | Treatment<sup>d</sup> |
|--------------------------|-----------------|-------------------------------|-----------------------|----------------------|---------------------|
| 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, GI, HYS, CPT, PLT, WBC, AKI, RBM | No                            |                        | Folate, fomepizole, NAC, thiamine, dexamethasone, neuromuscular blockers, propofol, phenobarbital, 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                            |                        | Benzo diazepines |
| 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                            |                        | NaHCO<sub>3</sub>, 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, NaHCO<sub>3</sub>, 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 |

<sup>a</sup> Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals Yes with known agent(s)

<sup>b</sup> Age in years unless otherwise stated

<sup>c</sup> AC anticholinergic, AG anion gap, AGT agitation, AKI acute kidney injury, ALI acute lung injury/ARDS, AP aspiration pneumonia, AVB AV block, BC bradycardia, BP bradypnea, CA cardiac arrest, CNS coma/CNS depression, CPT coagulopathy, DLM delirium, GIB GI bleeding, GIH intestinal ischemia, HAL hallucination, HPT hepatotoxicity, HT hypotension, HTN hypertension, 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, SYS sympathomimetic syndrome, SZ seizures, TC tachycardia, VD ventricular dysrhythmia, WBC leukocytosis

<sup>d</sup>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, NaHCO<sub>3</sub> 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

| Age / Gender | Clinical findings | Life support withdrawn | Brain death confirmed | Treatment reported |
|--------------|-------------------|------------------------|-----------------------|--------------------|
| 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 (norpinephrine), 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 | NaHCO₃, vasopressors (norpinephrine), 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 (norpinephrine), IV fluid resuscitation |
| Unknown M    | AK, SHS, HT, TC, BP, QRS, QTC, RD, CNS, MA, HPT, CPT, PLT, CA | No | | Folate, fomepizole, NAC, pyridoxine, NaHCO₃, thiamine, vasopressors (epinephrine, norpinephrine, vasopressin, dobutamine, phenylephrine, angiotensin II), CPR, ECMO, intubation, IV fluid resuscitation |
| Unknown M    | HT, TC, BP, MI, AP, CNS, MA, GIB, HYT, CPT, PLT, WBC, AKI, RBM | No | | None |
### Table 39 Most common drugs associated with adverse drug reactions

| Drug                        | 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               | 139 (54.9) |
| **Class total**             | **253 (100)** |

*a* Includes gabapentin, clonidine, methotrexate, acetaminophen, baclofen, tramadol, valproic acid, fentanyl, ziprasidone, metoprolol, hydroxyzine, benztpine, phenytoin, fluphenazine, ethanol, diphenhydramine, lorazepam, heroin, fluoxetine, nadolol, diltiazem, cocaine, tizanidine, trazodone, propranolol, carbamazepine, oxycodone, oxcarbazepine, cannabidiol, buprenorphine, celepime, arginine, fluconazole, flecanide, carvedilol, cefdinir, caripazine, cyclobenzaprin, enalapril, cytarabine (cytosine arabinoside), duloxetine, chlorhydrate, clomipramine, clonazepam, clozapine, diazepam, dextromethorphan, delta-9-tetrahydrocannabinol, cyclophosphamide, escitalopram, trifluoperazine, linezolid, palabresib, phenobarbital, pregabalin, procholorperazine, 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, lisdexametamine, zolpidem, loxapine, paroxetine, methadone, guanfacine, methylphenidate, metoclopramide, mitrazapine, morphine, naloxone, nitroprusside, nitrous oxide, and meperidine

### Table 40 Antidotal therapy

| Antidote                        | N (%) |
|---------------------------------|-------|
| 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) |
| Hydrococobalamin                | 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

| Antivenom                        | N (%) |
|----------------------------------|-------|
| Crotalidae polyvalent fab (ovine)| 109 (52.7) |
| Crotalidae immune fab2 (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)
antivenom in 2021. This continues to represent an upward trend (31.0% of cases in 2020) [4].

Table 42 Supportive care—pharmacologic

| Category                        | N (%) |
|--------------------------------|-------|
| 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) |
| Dexametomidine                 | 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)** |

*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

| Category                        | N (%) |
|--------------------------------|-------|
| IV fluid resuscitation         | 3540 (78.8) |
| Intubation/ventilatory management | 789 (17.6) |
| CPRb                           | 66 (1.5) |
| Transfusion                    | 41 (0.9) |
| ECMOc                          | 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)** |

*Percentages based on the total number of treatments administered (N=4495); 3769 registry cases (36.0%) received at least one form of nonpharmacologic treatment. Cases may have involved the use of multiple forms of treatment.

bCPR cardiopulmonary resuscitation
cECMO extracorporeal membrane oxygenation

dEDTA ethylenediaminetetraacetic acid

Table 44 Chelation therapy

| Chelation | N (%) |
|-----------|-------|
| DMSAb     | 10 (55.6) |
| BALc      | 3 (16.7) |
| EDTAd     | 3 (16.7) |
| Deferoxamine | 2 (11.1) |
| **Total** | **18 (100)** |

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

bDMSA dimercaptosuccinic acid
cBAL British anti-Lewisite (dimercaprol)
dEDTA ethylenediaminetetraacetic acid

Table 45 Supportive care—decontamination

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

*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%).
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.

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Declarations

Conflict of Interest JSL, DLK, MBS, LAF, AMK, SLC, SL, PMW, JB, KA: These authors have no conflicts of interest to report.

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References

1. Aldy K, Mustaqim D, Campleman S, Meyn A, Abston S, Krotulski A, et al. Notes from the Field: Ilicit Benzo diazepines Detected in Patients Evaluated in Emergency Departments for Suspected Opioid Overdose—Four States, October 6, 2020–March 9, 2021. Morb Mortal Wkly Rep. 2021;70(34):1177–1179.
2. Farah R, Kazzi Z, Brent J, Burkhart K, Wax P, Aldy K, et al. Ivermectin associated adverse events in the treatment and prevention of COVID-19 reported to the FACT pharmacovigilance project. Clin Toxicol (Phila). 2022;10:1–5. https://doi.org/10.1080/15563650.2022.2070187. Online ahead of print.
3. Brent J, Wax PM, Schwartz T, Kleinschmidt KC, Engebretsen K, Beuhler M, et al. The toxicology investigators consortium case registry—the 2010 experience. J Med Toxicol. 2011;7(4):266–76.
4. Spyres MB, Aldy K, Farrugia LA, Kang AM, Love JS, Campleman SL, et al. The Toxicology Investigators Consortium 2020 Annual Report. J Med Toxicol. 2021;17(4):333–362. https://doi.org/10.1007/s13181-021-00854-3.
5. Spyres MB, Farrugia LA, Kang AM, Aldy K, Calelo DP, Campleman SL, et al. The Toxicology Investigators Consortium Case Registry—the 2019 Annual Report. J Med Toxicol. 2020;16(4):361–387. https://doi.org/10.1007/s13181-020-00810-7.
6. Spyres MB, Farrugia LA, Kang AM, Calelo DP, Campleman SL, et al. The Toxicology Investigators Consortium Case Registry—the 2018 Annual Report. J Med Toxicol. 2019;15(4):228–254. https://doi.org/10.1007/s13181-019-00736-9.
7. Farrugia LA, Rhyee SH, Campleman SL, Judge B, Kao L, Pizon A, et al. The Toxicology Investigators Consortium Case Registry—the 2017 Annual Report. J Med Toxicol. 2018;14(3):182–211. https://doi.org/10.1007/s13181-018-0679-z.
8. O’Donnell J, Tanz L, Gladden RM, Davis NL, Bitting J. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyl—United States, 2019–2020. MMWR Morb Mortal Wkly Rep. 2021;70:1740–6. https://doi.org/10.15585/mmwr.mm7050e3.

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