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ORIGINAL ARTICLE

Adverse Drug Events and Reactions Managed by Medical Toxicologists: an Analysis of the Toxicology Investigators Consortium (ToxIC) Registry, 2010–2016

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Abstract

Introduction Adverse drug events/reactions (ADE/ADRs) cost more than $30 billion annually and are among the leading causes of death in the USA. Little is known about patients treated at the bedside for ADE/ADR by medical toxicologists.

Methods We conducted a retrospective study of ADE/ADR cases reported to the Toxicology Investigators Consortium (ToxIC) registry between January 1, 2010, and December 31, 2016. Clinical and demographic data were collected including age, sex, circumstances surrounding exposure, suspected offending substance, clinical manifestations, treatment, disposition, and outcome.

Results Among 51,440 ToxIC cases during this time period, 673 ADE/ADR cases were reported (337 females). By age, ADE/ADRs were seen most commonly among adults age 19–65 years (442/673, 65.7% of ADE/ADR) and older adults age 65–89 years (134/673, 19.9% of ADE/ADR). 222/673 (33%) of consults for ADE/ADR were seen in the emergency department (ED); 181/673 (26.9%) were seen in the hospital ward; and 160/673 (23.8%) were seen in the intensive care unit (ICU). The most commonly reported sign for ADE/ADR was tachycardia: 51/673 (7.6%), followed by bradycardia: 49/673 (7.3%). Most commonly reported agents associated with ADE/ADR were as follows: 97/673 (14.4%) due to cardiovascular medications; 76/673 (11.3%) due to antipsychotic medications; and 61/673 (9.1%) due to antidepressants. 429/673 (63.7%) of ADE/ADR were reported as due to a single agent, and 212/673 (31.5%) were reported as due to multiple agents.

Conclusions 4.2% of cases managed at the bedside by a consulting toxicologist and reported to the ToxIC registry between 2010 and 2016 had ADE/ADR as the reason for consultation. Agents most commonly involved in ADE/ADRs included cardiovascular medications, antipsychotic medications, and antidepressants.

Keywords Adverse drug reaction · Adverse drug event · Poisoning · Drug safety

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Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as a "noxious and unintended response to drugs occurring at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiologic function" [1]. ADE/ADRs contribute to hospitalization, inpatient events, morbidity, and mortality. These events may represent between the 4th and 6th leading cause of death in the USA, with an overall incidence of fatal ADE/ADR of 0.32% among hospitalized patients [2, 3]. Drugs most commonly reported in hospital admission for ADE/ADR include low-dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs (NSAID), and the most common presentation for ADE/ADR-related admission is gastrointestinal (GI) bleeding [4]. The incidence of serious ADE/ADR among hospitalized patients is estimated at 5%, with the two most common events being GI bleeding and CNS hemorrhage [5]. The drugs most commonly reported to cause in-hospital events include diuretics, opioid analgesics, and anticoagulants [2]. ADE/ADRs are associated with increased hospital length-of-stay and cost more than $30 billion per year in the USA [2, 6].

Age-based risk factors for ADE/ADR peak in a bimodal distribution. Alhawassi et al. reported a mean prevalence of ADE/ADR in the elderly population at 11% [7]. Similarly, ADE/ADRs are an important cause of childhood morbidity [8]. Female sex is also a risk factor for ADE/ADR. Physiological, hormonal, and genetic differences between males and females affect patients' response and rate of ADE/ADR, with female patients experiencing more frequent and more severe events [9].

Little is known about patients treated at the bedside for ADE/ADRs by medical toxicologists. We aimed to characterize ADE/ADR reported to the Toxicology Investigators Consortium (ToxIC) registry to inform next steps in tracking and managing these events.

Methods

We conducted a retrospective study of cases reported to the ToxIC registry between January 1, 2010, and December 31, 2016. ToxIC was established in 2010 and is maintained by the American College of Medical Toxicology. This registry collects prospective data on both outpatient and inpatient toxicology consults performed at the bedside in hospitals across the USA and in Israel [10]. Participating toxicology consult services represent about two-thirds of all medical toxicology training programs in the USA [10]. Participating sites enter de-identified data for cases of suspected poisoning evaluated and managed at the bedside by medical toxicologists [10].

We reported demographic and clinical variables including sex, race, age, reasons for exposure and consultation, exposure agents and routes, presenting clinical findings, treatments provided, disposition of the patient, and outcome. We excluded cases if there were data missing on age, sex, or reason for toxicologic consult. We included cases if they involved an ADE/ADR, which was coded as a dichotomous variable. Frequencies were used to report the characteristics of the study population.

ToxIC works under the approval of the Western Institutional Review Board (IRB) and participating sites obtain approval from their respective local IRB. This study was deemed non-human subjects research due to the characteristics of the data source and was therefore not subject to IRB review and approval.

Results

Among 51,440 cases reported to the ToxIC registry between 2010 and 2016, 35,263 cases were eliminated due to ADE/ADR status "unknown" or "missing." Among 16,177 cases included in the study, 673 were coded as ADE/ADR (see Fig. 1).

Table 1 displays case demographics stratified by patients with ADE/ADR versus patients with no ADE/ADR for during the study period. Cases aged 19–65 years represented the largest group by age: 65.7% of overall ToxIC cases and 65.7% of ADE/ADR cases. Although the age group 66–89 years

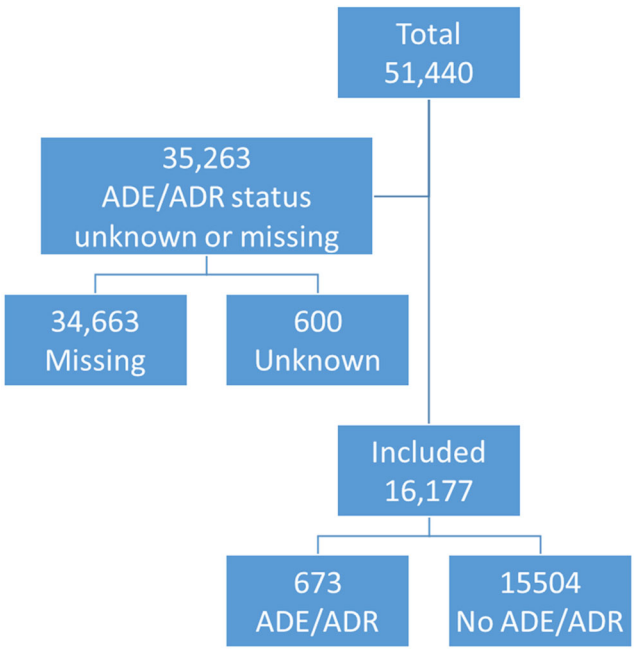

Fig. 1 Flowchart for ToxIC ADE/ADR cases 2010–2016

Table 1 Patient demographics stratified by ADE/ADR

Variable	Overall (n = 16,177)	ADE/ADR (= 673)	No ADE/ADR (n = 15,504)
Sex			
Male	8023 (49.6)	336 (49.9)	7687 (49.6)
Female	8154 (50.4)	337 (50.1)	7817 (50.4)
Age			
< 2 years	519 (3.2)	6 (0.9)	513 (3.3)
2–6 years	724 (4.5)	12 (1.8)	712 (4.6)
7–12 years	419 (2.6)	17 (2.5)	402 (2.6)
13–18 years	2927 (18.1)	51 (7.6)	2876 (18.6)
19–65 years	10,629 (65.7)	442 (65.7)	10,187 (65.7)
66–89 years	864 (5.3)	134 (19.9)	730 (4.7)
> 89 years	41 (0.3)	10 (1.5)	31 (0.2)
Unknown	54 (0.3)	1 (0.1)	53 (0.3)
Race			
American Indian/Alaska Native	143 (0.9)	–	143 (0.9)
Asian	288 (1.8)	12 (1.8)	276 (1.8)
Australian Aboriginal	1 (0.006)	–	1 (0.006)
Black/African	2172 (13.4)	95 (14.1)	2077 (13.4)
Caucasian	9216 (57)	420 (62.4)	8796 (56.7)
Mixed	160 (1)	8 (1.2)	152 (1)
Multiple races	2 (0.01)	–	2 (0.01)
Native Hawaiian/Pacific Islander	25 (0.2)	1 (0.1)	24 (0.2)
Other	780 (4.8)	28 (4.2)	752 (4.9)
Unknown/uncertain	3390 (21)	109 (16.2)	3281 (21.2)

Table 2 Location of encounter stratified by ADE/ADR

Variable	Overall (n = 16,177)	ADE/ADR (= 673)	No ADE/ADR (n = 15,504)
Location of encounter			
ED	5644 (34.9)	222 (33)	5422 (35)
Obs unit	181 (1.1)	14 (2.1)	167 (1.1)
Hospital floor	3615 (22.3)	181 (26.9)	3434 (22.1)
ICU	3745 (23.2)	160 (23.8)	3585 (23.1)
Outpatient/clinic/office consult	1115 (6.9)	20 (3)	1095 (7.1)
Missing	38 (0.2)	3 (0.4)	35 (0.2)
Multiple locations	1839 (11.4)	73 (10.8)	1766 (11.4)
ED and Obs unit	122 (0.8)	8 (1.2)	114 (0.7)
ED and Hosp floor	719 (4.4)	30 (4.5)	689 (4.4)
ED and ICU	630 (3.9)	19 (2.8)	611 (3.9)
ED and outpatient	5 (0.03)	–	5 (0.03)
Obs unit and Hosp floor	6 (0.04)	2 (0.3)	4 (0.03)
Obs unit and ICU	3 (0.02)	–	3 (0.02)
Obs unit and outpatient	1 (0.006)	–	1 (0.006)
Hosp floor and ICU	268 (1.7)	9 (1.3)	259 (1.7)
ED, Obs unit, and Hosp floor	3 (0.02)	1 (0.1)	2 (0.01)
ED, Hosp floor, and ICU	80 (0.5)	4 (0.6)	76 (0.5)
ED, Obs unit, Hosp floor, and ICU	2 (0.01)	–	2 (0.01)

Table 3 Presenting signs and agents stratified by ADE/ADR

Variable	Overall ($n = 16,177$)	ADE/ADR (= 673)	No ADE/ADR ($n = 15,504$)
Signs			
Bradycardia	360 (2.2)	49 (7.3)	311 (2)
Bradypnea	254 (1.6)	4 (0.6)	250 (1.6)
Hypertension	132 (0.8)	6 (0.9)	126 (0.8)
Hyperthermia	17 (0.1)	5 (0.7)	12 (0.08)
Hypotension	599 (3.7)	15 (2.2)	584 (3.8)
Multiple symptoms	797 (4.9)	62 (9.2)	735 (4.7)
Tachycardia	1407 (8.7)	51 (7.6)	1356 (8.7)
None	9379 (58)	439 (65.2)	8940 (57.7)
Agents			
Alcohol ethanol	830 (5.1)	9 (1.3)	821 (5.3)
Alcohol toxic	213 (1.3)	1 (0.1)	212 (1.4)
Amphetamine-like hallucinogen	17 (0.1)		17 (0.1)
Analgesic	2074 (12.8)	16 (2.4)	2058 (13.3)
Anesthetic	21 (0.1)	8 (1.2)	13 (0.1)
Anticholinergic/antihistamine	705 (4.4)	21 (3.1)	684 (4.4)
Anticoagulant	42 (0.3)	9 (1.3)	33 (0.2)
Anticonvulsant	478 (3)	56 (8.3)	422 (2.7)
Antidepressant	1333 (8.2)	61 (9.1)	1272 (8.2)
Antimicrobials	81 (0.5)	35 (5.2)	46 (0.3)
Antipsychotic	735 (4.5)	76 (11.3)	659 (4.3)
Cardiovascular	777 (4.8)	97 (14.4)	680 (4.4)
Caustic	130 (0.8)	1 (0.1)	129 (0.8)
Chemotherapeutic and immune	59 (0.4)	15 (2.2)	44 (0.3)
Cholinergic/parasympathomimetic	1 (0.006)	1 (0.1)	–
Cough and cold	140 (0.9)	5 (0.7)	135 (0.9)
Diabetic med	215 (1.3)	26 (3.9)	189 (1.2)
Endocrine	32 (0.2)	4 (0.6)	28 (0.2)
Envenomation	592 (3.7)	1 (0.1)	591 (3.8)
Foreign objects	6 (0.04)	–	6 (0.04)
Fungicide	1 (0.006)	–	1 (0.006)
Gases/vapors/irritants/dusts	204 (1.3)	1 (0.1)	203 (1.3)
GI	19 (0.1)	2 (0.3)	17 (0.1)
Herbals/dietary supps/vitamins	106 (0.7)	7 (1)	99 (0.6)
Herbicide	11 (0.1)	–	11 (0.1)
Household	141 (0.9)	–	141 (0.9)
Hydrocarbon	141 (0.9)	–	141 (0.9)
Insecticide	62 (0.4)	1 (0.1)	61 (0.4)
Lithium	267 (1.7)	56 (8.3)	211 (1.4)
Marine toxin	8 (0.05)	–	8 (0.1)
Metals	225 (1.4)	1 (0.1)	224 (1.4)
Opioid	1310 (8.1)	51 (7.6)	1259 (8.1)
Other nonpharmaceutical	51 (0.3)	4 (0.6)	47 (0.3)
Other pharmaceutical	35 (0.2)	3 (0.4)	32 (0.2)
Parkinson's med	11 (0.1)	1 (0.1)	10 (0.1)
Plants and fungi	125 (0.8)	3 (0.4)	122 (0.1)
Psychoactive	541 (3.3)	9 (1.3)	532 (3.4)
Pulmonary	11 (0.1)	1 (0.1)	10 (0.1)
Rodenticide	22 (0.1)	–	22 (0.1)

Table 3 (continued)

Variable	Overall ($n = 16,177$)	ADE/ADR (= 673)	No ADE/ADR ($n = 15,504$)
Sed-hypnotic/muscle relaxant	1288 (8)	43 (6.4)	1245 (8)
Sympathomimetic	796 (4.9)	11 (1.6)	785 (5.1)
WMD/NBC/riot	4 (0.02)	2 (0.3)	2 (0.01)
Unknown agent	119 (0.7)	2 (0.3)	117 (0.8)
Exposure type			
Single	9386 (58)	429 (63.7)	8957 (57.8)
Multiple	4683 (28.9)	212 (31.5)	4471 (28.8)

represented 5.3% of overall ToxIC cases, this age group represented 19.9% of ADE/ADR reported.

Table 2 displays location of encounter stratified by ADE/ADR versus no ADE/ADR. The ED was the most common site for both overall cases (34.9%) and for ADE/ADR (33%). 10.8% of ADE/ADR were seen by medical toxicologists in multiple hospital units.

Table 3 displays presenting signs and agents stratified by ADE/ADR versus no ADE/ADR. The most common signs associated with ADE/ADR were multiple signs (9.2%), tachycardia, defined by ToxIC as heart rate > 140 beats per minute (7.6%), and bradycardia, defined by ToxIC as heart rate < 50 beats per minute (7.3%). Cardiovascular medications were most commonly involved in ADE/ADR (14.4%), although were reported as the involved agent in only 4.8% of overall cases reported in ToxIC. Antipsychotics were reported as the involved agent in 11.4% of ADE/ADR and 4.5% of overall ToxIC cases. Antidepressants were involved in 9.1% of ADE/ADR and 8.2% of overall ToxIC cases.

Table 4 shows the presenting signs and exposure type (single versus multiple agent) by age group. Single exposures were more common in all age groups except age > 89 years.

Figure 2 shows presenting signs for ADE/ADR versus no ADE/ADR. Figure 3 juxtaposes frequency of ADE/ADR versus no ADE/ADR by age group. Figure 4 shows presenting signs by age group for ADE/ADR.

The agent classes most commonly involved in ADE/ADR cases differed by age group. For age < 2 years: cardiovascular medications ($N = 2$, 33.3%); anticholinergic/antihistamine ($N = 2$, 33.3%); sedative hypnotic/muscle relaxant ($N = 1$, 16.7%); and gastrointestinal medications ($N = 1$, 16.7%). For age 2–6 years: anticholinergic/antihistamine ($N = 2$, 16.7%); cough/cold medications ($N = 2$, 16.7%); analgesics ($N = 1$, 8.3%); anesthetic medications ($N = 1$, 8.3%); antipsychotics ($N = 1$, 8.3%); cardiovascular medications ($N = 1$, 8.3%); psychoactive medications ($N = 1$, 8.3%); sedative/hypnotics ($N = 1$, 8.3%); and sympathomimetics ($N = 1$, 8.3%). For age 7–12 years:

Table 4 Presenting signs and exposure type by age group for those who had an ADE/ADR

	Age category						
Variable	< 2 ($n = 6$)	2–6 ($n = 12$)	7–12 ($n = 17$)	13–18 ($n = 51$)	19–65 ($n = 442$)	66–89 ($n = 134$)	> 89 ($n = 10$)
Signs							
Bradycardia	–	2 (16.7)	2 (11.8)	5 (9.8)	20 (4.5)	18 (13.4)	2 (20)
Bradypnea	–	–	–	–	3 (0.7)	1 (0.7)	–
Hypertension	–	–	–	–	4 (0.9)	1 (0.7)	–
Hyperthermia	–	–	–	1 (2)	3 (0.7)	1 (0.7)	–
Hypotension	–	–	–	–	12 (2.7)	2 (1.5)	1 (10)
Multiple symptoms	2 (33.3)	–	2 (11.8)	2 (3.9)	31 (7)	22 (16.4)	3 (30)
Tachycardia	–	–	2 (11.8)	10 (19.6)	31 (7)	8 (6)	–
None	2 (33.3)	10 (83.3)	11 (64.7)	28 (54.9)	309 (70)	76 (56.7)	3 (30)
Exposure type							
Single	4 (66.7)	7 (58.3)	10 (58.8)	32 (62.7)	281 (63.6)	90 (67.2)	4 (40)
Multiple	2 (33.3)	4 (33.3)	7 (41.2)	18 (35.3)	138 (31.2)	38 (28.4)	5 (50)
NA	–	1 (8.3)	–	1 (2)	23 (5.2)	6 (4.5)	1 (10)

One patient had an unknown age so total *n* for this table is 672

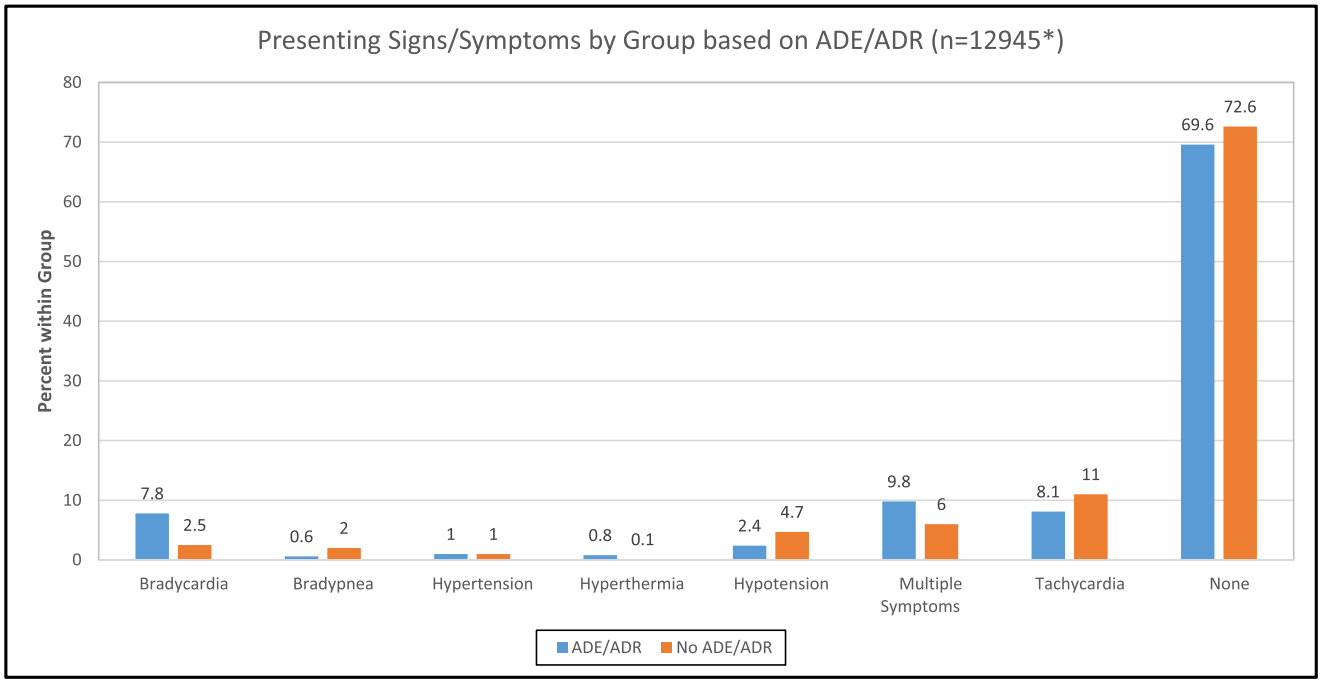

Fig. 2 Presenting signs/symptoms for cases with ADE/ADR. Note $n = 12{,}945$ are used for this figure, as this is the number of cases for which signs/symptoms were reported by the bedside toxicologist

antipsychotics ($N = 5$, 29.4%); antidepressants ($N = 3$, 17.6%); cardiovascular medications ($N = 3$, 17.6%); and lithium ($N = 2$, 11.8%). Age 13–18 years: antidepressants ($N = 11$, 21.6%); antipsychotics ($N = 10$ 19.6%); and sedative hypnotic/muscle relaxants ($N = 6$, 11.8%). Age 19–65 years: antipsychotics ($N = 50$, 11.3%); lithium ($N = 44$, 10%); anticonvulsants ($N = 44$, 10%); and opioids ($N = 42$, 9.5%). Age 66–89 years: cardiovascular medications ($N = 51$, 38.1%); antipsychotics ($N = 10$, 7.5%); and opioids ($N = 9$, 6.7%). Age > 89 years: cardiovascular medications

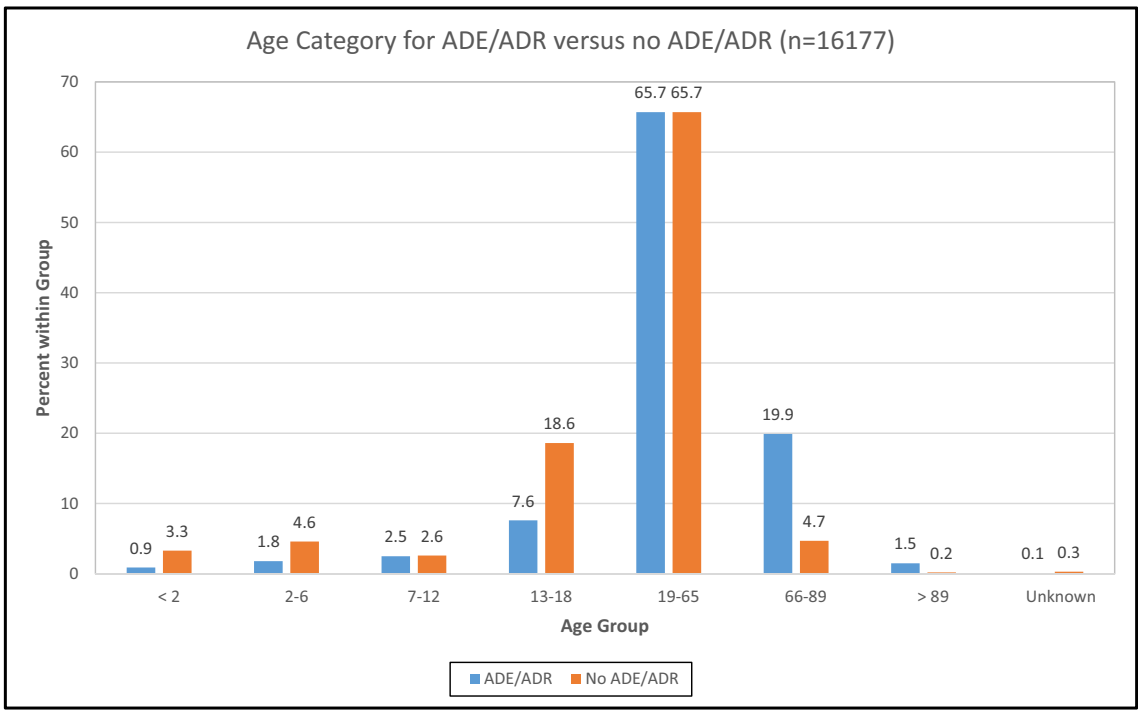

Fig. 3 Percent within each Age Category by Group (ADE/ADR and no ADE/ADR)

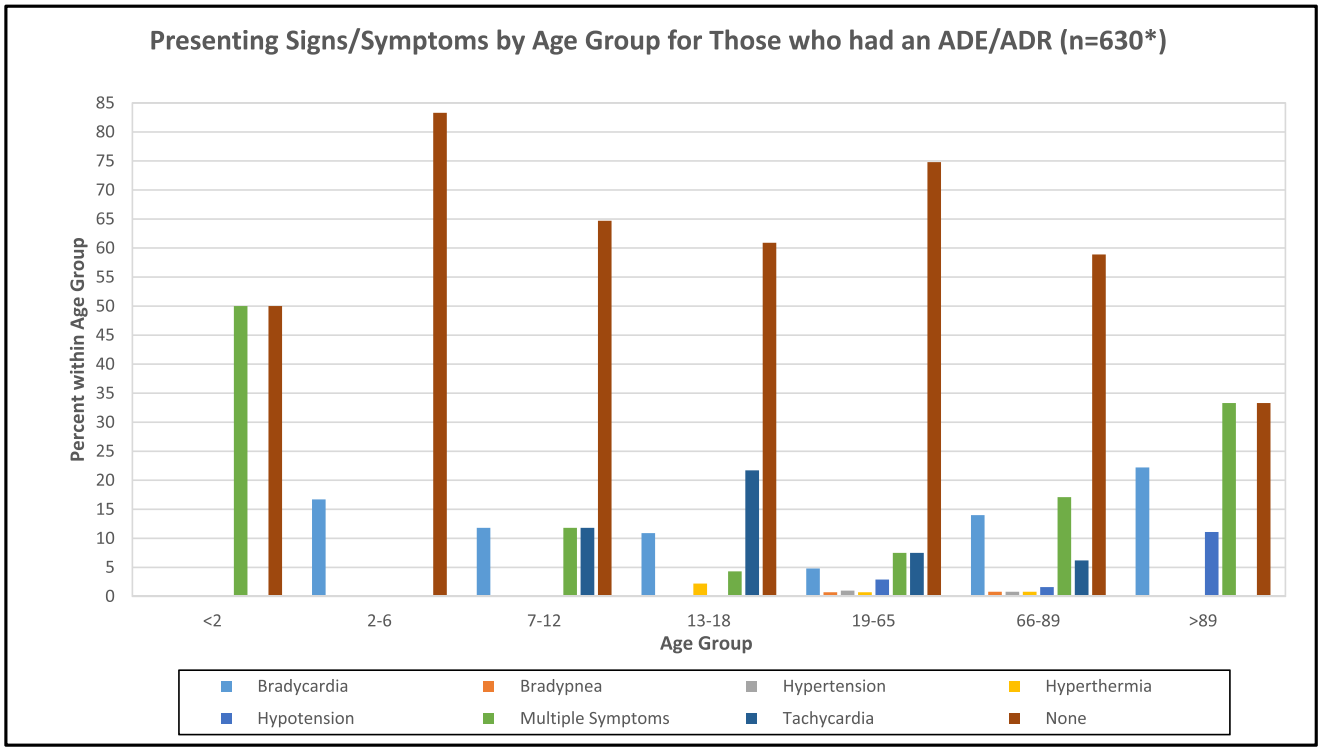

Fig. 4 Presenting signs/symptoms by age group for ADE/ADR cases. *$n = 630$ because one record was missing age and values of NA were excluded from the symptoms; therefore, the corresponding n for each group are as follows: < 2 $n = 4$; 2–6 $n = 12$; 7–12 $n = 17$; 13–18 $n = 46$; 19–65 $n = 413$; 66–89 $n = 129$; and > 89 $n = 9$

($N = 7$, 70%); psychoactive medications ($N = 1$, 10%); and antidepressant ($N = 1$, 10%).

Discussion

While this study of cases reported to the ToxIC registry found 4.2% of bedside consults performed by medical toxicologists were for ADE/ADR, previous reports of the incidence of ADE/ADR among hospitalized patients have varied: 3.2–5.64% [11]; 6.8–14% [12]; and 15.1% [3]. Shehab et al. reported that 4/1000 ED visits occurred for ADE/ADR and that the most common agents involved were opioid analgesics, anticoagulants, antibiotics, and diabetic medications; however, such reported data may miss subtle presentations for ADE/ADR [13]. Nickel et al. note that non-specific presentations to EDs by older adults may be related to ADE/ADR in 12.2% of patients [14]. Factors that may contribute to the large range in the incidence of ADE/ADR as reported in the literature include variation in definitions and inclusion criteria, and the fact that ADE/ADRs may not always be reported to an ADE/ADR registry. Despite the variable rate of ADE/ADR reported in the literature, toxicologists as well as medical providers in the ED, outpatient, and inpatient settings should be facile in the management of ADE/ADR.

Among all age groups in our study, the most common drug classes involved in ADE/ADR were cardiovascular medications, antipsychotics, and antidepressants. The frequency of ADE/ADR consults that involved these three drug classes was higher than the frequency among non-ADE/ADR consults. A previous study reported an ADR rate of 24.2% among admitted patients managed with cardiovascular drugs [15]. Antipsychotics are also associated with ADE/ADR and have been previously reported in roughly 18% of admitted patients treated with antipsychotics [16, 17]. Given the most commonly reported medications involved in ADE/ADR reported in the existing literature include aspirin, warfarin, diuretics, and NSAIDs [4], consults for ADE/ADR reported to ToxIC may not be representative of typical ADE/ADR.

Our finding that adults age 19–65 and older adults age 66–89 were most commonly evaluated at the bedside by a medical toxicologist for an ADE/ADR is consistent with existing literature that highlights the vulnerability of older adults to such events [7, 18, 19]. Older adults are particularly vulnerable to ADE/ADR due to polypharmacy, altered drug pharmacokinetic profiles, drug interactions, and cognitive problems [18]. In a recent study, cardiovascular drugs were the most common medications involved in drug-drug interactions affecting older adults [19]. This is consistent with our finding that cardiovascular medications were the class of drugs most commonly involved in ADE/ADR reported in cases age 66–89 years and > 89 years.

The use of medications in the pediatric population poses a challenge because safety data are limited by lack of clinical

trials and sparse information about changes in pharmacokinetics over time as children develop [8, 20]. Many pediatric ADE/ADRs are reported in infants under 1 year, with urticaria and other rashes being the most common manifestations [21]. The reported incidence of pediatric ADE/ADR is 10.9% in hospitalized children and 1.0% in children evaluated in the outpatient setting, with increased risk for infants, male sex, and children receiving greater than 4 medications [22]. In our study, multiple medication classes were involved in ADE/ADR in children including cardiovascular, anticholinergic/antihistamines, sedative hypnotic/muscle relaxants, cough/cold, analgesic, anesthetic, sympathomimetic, antipsychotic, psychoactive, antidepressant, and lithium. ADE/ADRs to sympathomimetic medications in children warrant further study given these medications are commonly prescribed and have a known risk of adverse effects [23].

Recently, the US National Institutes of Health (NIH) implemented a policy to integrate the role of sex as a biological variable into research design, analysis, and reporting, allowing for integration of potential sex effects into biomedical research [24]. It is reported in the literature that physiological, hormonal, and genetic differences between males and females are likely factors in higher serum drug concentrations as well as more frequent, and more severe ADE/ADR [9]. However, in the current study, when assessing frequency of ADE/ADR by sex, we did not find differences.

Some study limitations merit mention. While each participating site is encouraged to enter all encountered cases, ToxIC data relies on voluntary reporting by medical toxicology services, and consultation patterns may vary widely between sites that participate. The ToxIC registry relies on reporting by medical toxicologists and as such, the data may not differentiate ADE/ADR from confounding presentations such as therapeutic misadventure, polypharmacy, organ system dysfunction unrelated to medication, or comorbid acute or chronic disease. It is possible that the ToxIC registry records higher acuity exposures for which a medical toxicology service has been consulted. Thus, registry cases may not be representative of or generalizable to the broader pool of drug exposures, the majority of which may be managed by other healthcare providers such as general practitioners, emergency medicine physicians, pediatricians, clinical pharmacologists, or poison center staff. Analysis of these data is limited by missing data. For example, many ADE/ADRs reported to the ToxIC registry during this time period had no signs listed. This may be due to missing data, or due to abnormal signs that were below the threshold for reporting. For example, ToxIC defines tachycardia as heart rate > 140 beats per minute. While a heart rate of 120 beats per minute is technically abnormal in adults, a heart rate below 140 beats per minute would not be categorized as tachycardia in the ToxIC registry, thus potentially resulting in the underestimation of cardiovascular adverse effects. Our ability to analyze and interpret registry data was limited by the restricted nature of data gathered and limited ability to determine causality. For example, we typically do not have access to tissue biopsy results, real-time probability scale score for ADE/ADR (e.g., Naranjo ADR probability scale), results of challenge tests, or comprehensive toxicologic testing results. Following the completion of this analysis, the ToxIC registry implemented the Naranjo ADE/ADR Probability Scale as part of data collection, which explores association between exposure and subsequent ADE/ADR [25–27]. Finally, whether the ADE/ADR was the reason for presentation to the medical facility; reason and context for medication use; when signs of toxicity occurred; and where the consult took place within the time course of the patient's stay at the facility are not collected by the ToxIC registry.

Conclusions

In reviewing 51,440 cases managed at the bedside by medical toxicologists and reported to ToxIC between 2010 and 2016, we found that 4.2% of cases were reported as ADE/ADR. An ADE/ADR more commonly involved adults, and types of agents involved in ADE/ADR differed by age.

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Compliance with Ethical Standards

ToxIC works under the approval of the Western Institutional Review Board (IRB) and participating sites obtain approval from their respective local IRB. This study was deemed non-human subjects research due to the characteristics of the data source and was therefore not subject to IRB review and approval.

Conflicts of Interest None.

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