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Emergency Department Visits for Adverse Drug Reactions Involving Alcohol: United States, 2005–2011

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Abstract

Background—Alcohol consumption may interfere with absorption, distribution, metabolism, and excretion of medications and increase risk of adverse drug reactions (ADR). Studies report increasing prescription medication use over time, with many U.S. drinkers using alcohol-interactive medication. This study identifies trends in incidence of U.S. emergency department (ED) visits for ADR with alcohol involvement (ADR-A), compares characteristics and disposition between ADR-A visits and ADR visits without alcohol involvement (ADR-NA), and examines frequency of implicated medications in such visits for 2005–2011.

Methods—ADR visits were identified through the Drug Abuse Warning Network, a national surveillance system monitoring drug-related ED visits. Analysis accounted for sampling design effects and sampling weights. Estimates are presented for totals (ages 12+), age group, and/or sex. Trends were assessed by joinpoint log-linear regression. Differences between ADR-A and ADR-NA visits were compared using two-tailed Rao-Scott chi-square tests.

Results—From 2005 to 2011, incidence of ADR-A visits increased for males and females ages 21–34 and females ages 55+. An average of 25,303 ADR-A visits ages 12+ occurred annually. Compared with ADR-NA visits, ADR-A visits were more likely to involve males, patients ages 21–54, and 2+ implicated drugs. Alcohol involvement increased odds of more serious outcomes from ADR visits. CNS agents were the most common medications in ADR-A visits (59.1%), with nearly half being analgesics (mainly opioid). About 13.8% of ADR-A visits involved psychotherapeutic agents, including antidepressants. Besides CNS and psychotherapeutic agents, ADR-A visits involved a higher percentage of genitourinary-tract agents (mainly for impotence) than ADR-NA visits. Sex and age variations were observed with certain implicated medications.

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Conclusion—ED visits for alcohol–drug interactions can be prevented by avoiding alcohol when taking alcohol-interactive medications. Our results underscore the need for health care professionals to routinely ask patients about alcohol consumption and warn of ADR risks before prescribing and dispensing alcohol-interactive medications.

Keywords

Adverse drug reactions; alcohol; sex differences; age differences; emergency department visits

Introduction

Alcohol may interact with prescription medications and increase the risk of adverse drug reactions (ADR). Through pharmacokinetic and pharmacodynamic interactions, alcohol interferes with the absorption, distribution, metabolism, and excretion of medications and can have additive or antagonistic effects, particularly in the central nervous system (CNS) (Tanaka, 2003; Weathermon and Crabb, 1999). Acute alcohol consumption leads to competition for drug-metabolizing enzymes, increasing the available drug supply to the body as well as the risk of side effects, while chronic alcohol use activates drug-metabolizing enzymes, decreasing the availability and effects of the drug (Jones, 2003; Sellers and Holloway, 1978; Tanaka, 2003; Weathermon and Crabb, 1999). Because of these interactions, concurrent users of alcohol and alcohol-interactive medications may experience adverse short-term side effects including drowsiness, nausea, and vomiting, as well as long-term side effects such as internal bleeding, gastrointestinal issues, and severe liver damage, which could lead to death (Jones et al., 2014; Kaufman et al., 1999; Moore et al., 2015).

The percentage of Americans who reported taking at least 1 prescription drug in the past month increased from 43.5% in 1999–2000 to 48.3% in 2007–2008; and the percentage for taking 2 or more drugs and 5 or more drugs increased from 25.4% to 31.2% and 6.3% to 10.7%, respectively (Gu et al., 2010). The reasons for such increases include, but are not limited to, new drug development, insurance coverage expansion, and growing pharmaceutical marketing and advertising (National Center for Health Statistics [NCHS], 2014). CNS stimulants and antidepressants are reported as the most commonly used prescription drugs for adolescents ages 12–19 and adults ages 20–59, respectively (Gu et al., 2010), and both of these drug types are known to interact with alcohol (National Institute on Alcohol Abuse and Alcoholism, 2014). Over a 12-year period (1999–2010), an average of 41.5% of current drinkers 20 years and older reported taking at least one alcohol-interactive prescription medication (Breslow et al., 2015). Over the same time period, an average of 77.8% of current drinkers 65 years and older also reported doing so. The increase in prescription medication use over time and the large percentage of drinkers using alcohol-interactive medication raise a concern about whether adverse side effects caused by alcohol–drug interactions have increased over time, especially those severe episodes that require immediate medical attention.

The National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance is a U.S. surveillance system initiated under the collaboration of the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention, and the

Consumer Product Safety Commission that has operated since 2004. This surveillance system has collected information on emergency department (ED) visits attributed to adverse drug events in a nationally representative sample of hospitals (63 participating hospitals reporting a total of around 10,600 cases per year; Budnitz et al., 2006). Unfortunately, this surveillance excluded alcoholic beverages, so it cannot be used to examine the adverse side effects caused by alcohol–drug interactions. The Drug Abuse Warning Network (DAWN), a U.S. national surveillance system administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), collected information, including alcohol involvement, from drug-related ED visits. DAWN reported an 84% increase in the weighted annual estimates of ED visits resulting from adverse reactions to pharmaceuticals over a 7-year period, from 1.3 million visits in 2005 to 2.3 million visits in 2011 (Center for Behavioral Health Statistics and Quality [CBHSQ], 2013a). Although alcohol information is collected in DAWN, little attention has been paid to alcohol involvement in ADR. To the best of our knowledge, no research has examined the difference in characteristics and implicated medications between ADR with alcohol involvement (ADR-A) and ADR without alcohol involvement (ADR-NA).

The objective of this study was thus to analyze DAWN data to identify the trends in incidence of ED visits for ADR-A over time, compare the characteristics and disposition between ADR-A and ADR-NA, and examine frequency of implicated medications in such visits in the United States for 2005–2011.

Materials and Methods

Data Source

DAWN public use data files for 2005–2011 (i.e., the final year of DAWN) were obtained from the Substance Abuse and Mental Health Data Archive. DAWN collected information from the medical records of drug-related ED visits in sampled non-Federal, short-stay, general surgical and medical hospitals with at least one 24-hour ED (CBHSQ, 2013b). DAWN employs a stratified simple random sampling design to select hospitals, with oversampling in selected metropolitan areas. Within each selected hospital, ED visits on selected days of the month are reviewed by a trained DAWN reporter to identify any visits that recorded recent drug use as either a direct cause or a contributory factor. The number of participating hospitals ranges from 205 in 2006 to 242 in 2009, resulting in a sample of drug-related ED visits ranging from 229,211 visits in 2011 to 383,977 visits in 2008 (SAMHSA, n.d.). Details on the survey design and implementation can be found in the DAWN methodology report (CBHSQ, 2013b). Although overall visits weighted response rates are relatively low (ranging from 26.1% in 2006 to 35.2% in 2011), DAWN offers the only national ED data with detailed information on related drug and alcohol involvement. These data have been widely used by U.S. officials and health professionals to monitor national trends on substance use and ED visits.

Case Identification

DAWN reporters retrospectively reviewed a patient's chief complaint, physician's/nurse's/clinician's assessment, and/or diagnosis details on a selected ED medical record to determine

whether such record is a DAWN case. Following the predetermined case decision tree (p. 22, CBHSQ, 2013b), DAWN reporters assigned each ED visit to the first applicable case type in the following order—(1) drug-related suicide attempt, (2) seeking detoxification, (3) underage alcohol use only, (4) adverse reaction, (5) overmedication, (6) malicious poisoning (e.g., drug facilitated assault, rape, or homicide), (7) accidental ingestion, and (8) others.

This study focused on the fourth case type—adverse reactions, referred to below as ADR, which were those visits not applicable to the first three case types but meeting the criterion that “the patient had an ‘adverse reaction’ to a prescription drug, over-the-counter medication, or dietary supplement taken as prescribed or recommended.” These ADR cases include adverse side effects, allergic reactions, drug–drug interactions, and drug–alcohol interactions experienced when drugs are taken for therapeutic purposes as prescribed or directed. Based on alcohol involvement, the ADR cases were categorized into two groups for comparison—ADR-A and ADR-NA.

Drug Classification

The DAWN Drug Reference Vocabulary (DRV) uses the Multum *Lexicon*, © 2012, to classify drug types and modifies it to include illegal drugs, inhalants, and alternative medicines. DAWN DRV enables identification of more than 3,300 generic drugs and presents a tiered structure that assigns individual drugs to higher-level groupings. Reporters used DAWN DRV to report up to 16 (in 2005–2008) or 22 (in 2009–2011) related drugs per visit to DAWN. Drugs deemed by the ED medical staff to be unrelated to the ED visit were not included. Alcohol information was collected when alcohol was involved in addition to drugs, or when alcohol was consumed by patients under the age of 21. The DAWN contractor performed deduplication to ensure an individual drug appears only once for a visit. All drug data reported in previous years were recoded using the most recent classification system to ensure that the estimates were comparable over data years. Detailed information on data quality assurance and quality control can be found in the DAWN methodology report (CBHSQ, 2013b).

In this study, the number of implicated drugs in a visit was counted based on the number of reported individual drugs (including prescription medications, over-the-counter drugs, alternative medicines, and illegal drugs), excluding alcohol. Illegal drug involvement in ADR visits was relatively rare, and the percentage estimates were imprecise.

Visit Characteristics and Disposition

DAWN collected patient demographic characteristics including sex, age, and race/ethnicity. Patients under the age of 12 were excluded from this study, because they had a small prevalence of alcohol consumption. Age was further categorized into 4 groups (12–20, 21–34, 35–54, and 55+) to offer reliable estimates and to examine potential age variations. Race/ethnicity information was not used in this study because of its low-quality reporting and high percentage of missing data (about 15% each year) (CBHSQ, 2013b).

Visit disposition was categorized into three main groups (CBHSQ, 2014)—(1) less serious outcomes, including normal discharge, released to police/jail, and referred to detox or another treatment; (2) more serious outcomes, including admission to the same hospital,

transfer to another health care facility, and deaths occurring in the ED; (3) all other dispositions, including left against medical advice, not documented, and other.

Statistical Analysis

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and took into account sampling design effects and sampling weights. Variances were computed based on the Taylor series linearization method, assuming a without-replacement design. The estimates were considered imprecise and thus suppressed if (1) the relative standard error (i.e., standard error divided by estimate) is greater than 50%, (2) the lower bound of the 95% confidence interval includes zero, or (3) estimates are based on fewer than 30 visits (CBHSQ, 2013b). Estimates are presented for total (ages 12+), and by age group and/or sex. ED visits missing information on age or sex were excluded from analysis (i.e., 1,794 visits missing age only, 4,215 visits missing sex only, and 274 visits missing sex and age in 2005–2011). Because the main interest of this study is on alcohol–medication interactions, we excluded ADR visits that did not involve pharmaceuticals. The final analytic sample sizes for ages 12+ in 2005–2011 combined were 177,121 visits for ADR-A and 12,190,717 visits for ADR-NA.

Incidence of ED visits for ADR-A was calculated as the estimated number of ED visits for ADR-A, divided by annual population estimates obtained from NCHS, and multiplied by 100,000. Trends for overall incidence (ages 12+) and for age- and sex-specific incidence over time were assessed by the Joinpoint Regression Program (National Cancer Institute, 2015) and fitted into a simplest joinpoint log-linear regression model, weighted by the square of the estimate divided by the variance at each time period. An apparent change in trend was tested by a sequence of permutation test at the 0.05 significance level (Kim et al., 2000).

Characteristics of ED visits were compared between ADR-A and ADR-NA visits by using two-tailed Rao-Scott chi-square test. Logistic regression models, stratified by sex and adjusted for other characteristics, assessed the associations between alcohol involvement and disposition (more serious outcomes vs. less serious outcomes). All other dispositions were excluded because their outcome seriousness was unknown. Data year was included in the models to control for the potential temporal changes.

In this study, we followed *DAWN Trend Tables* (CBHSQ, 2013c) and used the tiered classification of the “standard drug list” (a shorter list of about 500 drugs) for analysis. Therapeutic medications mentioned in each visit were first examined based on the second tier of the classification scheme (i.e., ED standard drug list 2, SDLED_2). Because a single visit can have multiple implicated medications, a visit can be assigned to more than one therapeutic medication class. Differences in therapeutic medication classes involved in adverse-reaction ED visits were examined between ADR-A and ADR-NA visits. The differences were determined to be statistically significant at the 0.05 level using two-tailed Rao-Scott chi-square tests without correction for multiple comparisons.

Results

Trends in Incidence of ED Visits

From 2005 to 2011, incidence of ED visits for ADR-A increased from 5.6 (95% confidence interval [CI] = 3.7–7.6) to 11.6 (95% CI = 6.4–16.8) visits per 100,000 population ages 12+; joinpoint regression estimated an average of 10.7% increase per year (95% CI = 1.0%–21.4%). Males had higher incidence and a relatively larger increase in incidence over time than females (Figure 1, Age 12+), although both trends for males and females did not reach statistical significance ($p = 0.06$ and 0.09 , respectively). Broken down by age group, a statistically significant increase in incidence over time was observed for males ages 21–34 (from 7.0 [95% CI = 3.8–10.2] to 19.6 [95% CI = 7.1–32.1], $p = 0.02$), females ages 21–34 (from 3.8 [95% CI = 1.9–5.7] to 10.2 [95% CI = 4.3–16.1], $p = 0.03$), and females ages 55+ (from 4.8 [95% CI = 2.3–7.3] to 7.2 [95% CI = 3.0–11.4], $p = 0.04$).

Characteristics and Disposition

In 2005–2011, an estimated average of 25,303 ED visits (ages 12+) per year resulted from ADR-A, which was about 1.4% of all ADR visits (Table 1). Compared with ADR-NA visits, ADR-A visits were more likely to involve males, patients ages 21–34 and 35–54, and have 2 or more implicated drugs. However, when stratified by sex, the number of implicated drugs was not statistically significantly different between ADR-A and ADR-NA among males.

Of ADR-A visits, 25.4% resulted in a more serious outcome, compared with 22.6% of ADR-NA visits (Table 1). Controlling for all other characteristics and data year, alcohol involvement increased the odds of a more serious outcome from ADR visits in both males (adjusted odds ratio [aOR] = 1.41, 95% CI = 1.16–1.71) and females (aOR = 1.60, 95% CI = 1.25–2.05) (Table S1). Additional adjustment for illegal drug involvement did not change aORs of alcohol involvement (data not shown).

Implicated Therapeutic Medications

Overall, the involvement patterns of implicated therapeutic medication classes were different between ADR-A and ADR-NA visits (Table 2). CNS, Psychotherapeutic, and genitourinary-tract agents were more likely to be involved in ADR-A visits, while cardiovascular agents, anti-infectives, coagulation modifiers, hormones, and other medication classes were more likely to be involved in ADR-NA visits. CNS agents were involved in more than 50% of ADR-A visits in both males and females and across all age groups, whereas CNS agents were involved in less than one third of ADR-NA visits. For patients ages 12–54, psychotherapeutic agents were the second most commonly involved medication class in ADR-A visits and were more common in ADR-A than in ADR-NA visits. For those ages 55 and older, cardiovascular agents were the second most commonly involved in ADR-A visits, but this involvement was not significantly different between ADR-A and ADR-NA. Almost all ADR-A visits involving genitourinary-tract agents were males, and about one third were ages 55 and older.

Within the class of CNS agents, analgesics were involved in 28.4% of the ADR-A visits, mainly opiates/opioids in 17.4%. Anxiolytics, sedatives, and hypnotics were involved in

24.7% of the ADR-A visits, mainly benzodiazepines in 16.7% (Table 3). Nonsteroidal anti-inflammatory agents were more commonly involved in ADR-A than ADR-NA visits for patients ages 55 and older only. The involvement of anxiolytics, sedatives, and hypnotics was more common in female ADR-A visits (30.8%) than in male ADR-A visits (20.5%). It is worth noting that CNS stimulants were involved in 11.4% of ADR-A visits for those ages 12–20.

Within the class of psychotherapeutic agents, antidepressants and antipsychotics were involved in 8.6% and 6.1% of ADR-A visits, respectively (Table 3). Although antidepressants were more commonly involved in ADR-A than ADR-NA visits for all patients but those ages 35–54, antipsychotics appeared to be more commonly involved in ADR-A than ADR-NA visits among those ages 35–54 only.

Within the class of genitourinary-tract agents involved in ADR-A (680 visits), almost all (655 visits) involved impotence agents, accounting for 4.4% of all male ADR-A visits and 3.0% of ADR-A visits for patients ages 55 and older (Table 3). Other common types of genitourinary-tract agents involved in ADR-NA were urinary antispasmodics (4,172 visits) and other miscellaneous agents (3,754 visits), which were not common in ADR-A visits (less than 20 visits per drug type).

Discussion

Along with the increase in American prescription drug use, findings from this study indicate that between 2005 and 2011, the incidence of ED visits for ADR-A increased from 5.6 to 11.6 visits per 100,000 population ages 12+. During the same time period, incidence of all drug-related ED visits (including those attributed to misuse or abuse of pharmaceuticals, illicit drug use, and underage drinking) increased from 1,131.3 to 1,790.1 visits per 100,000 population ages 12+ (CBHSQ, 2013c). Gender- and age-specific incidences of ADR-A visits significantly increased in males and females ages 21–34 and females ages 55 and older. According to research, the largest increase in adult (ages 20+) prevalence of taking 5 or more prescription drugs between 1999–2000 and 2011–2012 was observed in the age group of 20–39 (prevalence ratio = 4.6, 95% CI = 2.5–7.9) (Kantor et al., 2015). The overall high prevalence of current drinking among those ages 21–34 (SAMHSA, 2012), the increase in polysubstance use (Kantor et al., 2015), and the increase in prevalence of current drinking over time among females ages 21–34 and 55 and older (White et al., 2015) may partly contribute to this rise in ED visits.

In 2005–2011, an estimated annual average of 25,303 ED visits resulted from ADR-A. Compared with ADR-NA visits, ADR-A visits were more likely to involve males, patients ages 21–54, and have 2 or more implicated drugs. Greater quantity, higher frequency, and stronger intensity of alcohol consumption and a longer duration of excessive drinking can increase the risk of alcohol–drug interactions among drinkers taking alcohol-interactive medications. Males compared with females, and persons ages 21–54 compared with those ages younger than 21 or older than 54, generally drank more frequently and in higher quantities (Chan et al., 2007; Chen et al., 2004/2005; Kanny et al., 2013; Karlamangla et al., 2006; SAMHSA, 2012; White et al., 2015; Wilsnack et al., 2009). Some exceptions were

observed. The average drinking frequency and prevalence of drinking five or more days a week increased with age among drinkers (Chen et al., 2004/2005; Wilsnack et al., 2009), and the highest frequency of binge drinking was observed among binge drinkers ages 65 and older (Kanny et al., 2013). The findings on more implicated drugs may be attributed to the additive or unexpected pharmacological effects caused by polydrug use in combination with alcohol (Jones, 2003; Weathermon and Crabb, 1999). Our findings also showed that alcohol involvement increased the odds of a more serious outcome from ADR visits. CNS, psychotherapeutic, and genitourinary-tract agents were more likely to be involved in ADR-A visits, while cardiovascular agents, anti-infectives, coagulation modifiers, hormones, and other medication classes were more likely to be involved in ADR-NA visits.

CNS agents were the most common medication class involved in ADR-A visits (59.1%). Nearly half of CNS agents involved were analgesics, mainly opioid. In 2007–2010, 10.5% of American adults ages 18–64 and 17.5% of ages 65 and older took at least one analgesic agent in the past 30 days (NCHS, 2014). Sites and colleagues (2014) estimated 89.2 million opioid prescriptions were written in 2010, an increase of 104% from 2000. Mixing opioid analgesics with alcohol can lead to dangerous side effects. Alcohol enhances the inhibitory effects of opioids on *N*-methyl-D-aspartate receptors, increasing sedation and leading to drowsiness and the potential reduction of breathing functions and the cough reflex (Weathermon and Crabb, 1999). Although FDA requires warning labels for opioid medications stating these side effects (FDA, 2015), it is still necessary for health care professionals to inform their patients of the risks of concomitant use of opioids and alcohol before prescribing such drugs. Prevalent use of opioid analgesics and alcohol among American adults without proper supervision by health care professionals can increase their risks of having severe alcohol–drug reactions and requiring immediate medical attention.

Psychotherapeutic agents, including antidepressants, were involved in 13.8% of ADR-A visits. Previous studies show that alcohol use disorder (AUD) was associated with major depressive and bipolar I disorders and antisocial and borderline personality disorders (Grant et al., 2015), and that bupropion was one of the most commonly used prescription drugs among primary care patients with AUD (Brown et al., 2007). Excessive alcohol consumption and sudden cessation of alcohol consumption among wellbutrin (bupropion hydrochloride) users may increase their risk of having seizures (FDA, 2009). It is crucial for health care professionals to monitor alcohol consumption among high-risk populations such as those with comorbidities, and to be well informed about all prescribed medications for each condition. The increased risk for ADR among those with AUD and depression can foster the exploration and use of alternative treatments such as cognitive-behavioral therapy and motivational interviewing (Riper et al., 2014).

Self-medication with alcohol has been observed among those with mood, anxiety, or posttraumatic stress disorders (Bolton et al., 2009; Robinson et al., 2009a; Leeies et al., 2010). Individuals with anxiety disorders and self-medication behaviors had significantly higher odds of seeing a professional and being prescribed drugs than those with anxiety disorders but without self-medication behaviors (Robinson et al., 2009b). Though patients may take their psychotherapeutic or other drugs as prescribed or directed by their physicians, they may drink alcohol at the same time to cope with their symptoms and potentially

increase their risk of having adverse alcohol–drug interactions if the medications taken are alcohol-interactive.

Different absorption and metabolism rates of alcohol and drugs between males and females can contribute to sex differences in alcohol–drug interactions (Harris et al., 1995; Thomasson, 1995). After consuming the same amount of alcohol, females are more likely to achieve higher blood alcohol concentrations than males because females have less gastric alcohol dehydrogenase activity and proportionally less body water (Frezza et al., 1990; Thomasson, 1995). Our study found that female ADR-A visits, compared with those of males, had a higher percentage of involvement of anxiolytics, sedatives, and hypnotics, mainly benzodiazepines (females vs. males: 21.2% vs. 13.6%). This sex difference was not apparent in ADR-NA visits (females vs. males: 2.7% vs. 2.4%), so the sex difference observed in ADR-A visits was unlikely caused by different prescription rates between males and females alone. Our results also showed that female ADR-A visits had a higher number of implicated drugs than those visits for males. Females compared with males have higher prevalence of taking 3 or more and 5 or more prescription drugs, as well as higher prevalence of using anxiolytics, sedatives, and hypnotics (NCHS, 2014). Polydrug use or combined use with alcohol can increase the severity of adverse reactions of benzodiazepines (Weathermon and Crabb, 1999). A DAWN report showed that ED visits involving benzodiazepines in combination with opioids or alcohol had more serious outcomes than visits involving benzodiazepines alone (CBHSQ, 2014). As an FDA document noted, “fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality” (FDA, 2011a).

Our results showed that impotence agents were implicated in almost all ADR-A visits involving genitourinary-tract agents, and about one third involved males ages 55 and older. Alcohol consumption is positively correlated with sexual activity among older male Americans (Bach et al., 2013), and 4.2% of sexually-active male drinkers (ages 18 and older) regularly consumed alcohol before sex (Eaton et al., 2015). It is important for health care professionals to discuss the risks of concomitant use of impotence agents and alcohol with their male patients. For example, “[p]atients should be made aware that both alcohol and CIALIS [tadalafil] . . . act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. . . . [S]ubstantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache” (FDA, 2011b).

People age 65 and older have higher prevalence of taking multiple medications (NCHS, 2014), and current drinkers age 65 and older have higher prevalence of taking at least one alcohol-interactive prescription medication (Breslow et al., 2015). Because older people metabolize alcohol more slowly and have less body water compared with younger people, the bioavailability of alcohol increases when consuming the same amount of alcohol (Weathermon and Crabb, 1999). Due to these age-related changes in absorption, distribution,

and metabolism of alcohol and drugs, those who are older are at higher risk for adverse reactions even to medications with relatively low risks of side effects (Moore et al., 2007). For example, in our study, ADR-A visits among those ages 55 and older had a higher percentage of involvement of nonsteroidal anti-inflammatory agents than ADR-NA visits of patients the same ages (ADR-A vs. ADR-NA: 5.9% vs. 2.3%), while this difference was not observed in other age groups.

Children and adolescents with attention deficit hyperactivity disorder (ADHD) are often prescribed CNS stimulants, such as methylphenidate, dextroamphetamine, and amphetamine-dextroamphetamine, to reduce their symptoms (Barkla et al., 2015; Wolraich et al., 2011). Although research showed only a small increase in side effects when ADHD medications were taken with alcohol (Barkla et al., 2015), our results showed that 11.4% of ADR-A visits among those ages 12–20 involved CNS stimulants. ADHD medication users compared with nonusers had higher prevalence of psychiatric conditions, other medical conditions, and other psychotropic medication use (Cooper et al., 2011). Polydrug use in combination with alcohol could increase the risk of adverse reactions that would not be observed when the drug was administered alone. Diagnosis and medication treatment of ADHD have increased significantly over time among children ages 4–17 (Visser et al., 2014). Because adolescents and young adults ages 18–20 may be reluctant to disclose their drinking habits to their health care professionals since underage drinking is illegal, it is necessary to continue to monitor adverse reactions of ADHD medications in combination with alcohol.

Several limitations of this study need to be noted. DAWN's overall weighted response rates are relatively low, which might have resulted in nonresponse bias if the patterns of drug or alcohol involvement differed by hospital participation status. It is possible that specific drugs regularly taken as prescribed by a health care provider might have been over- or underreported in this study, especially when their contribution to the ED visits was uncertain or unclearly documented. A prospective observational study showed that emergency physicians only categorize 61.4% of ADR cases as medication related (Hohl et al., 2010), meaning some ED visits might not have been categorized as ADR cases in DAWN. Although DAWN reporters attempted to record the specific drugs involved using DAWN DRV, some medications might have been reported using a broader drug category when a general description of drugs was listed on the medical charts (CBHSQ, 2013b). Comorbidities and insurance coverage that could affect seriousness of the outcomes of ADR visits were not controlled for in our logistic regression models, because no such information was available in the DAWN public use data files (CBHSQ, 2014).

ED visits caused by alcohol–drug interactions can be prevented by avoiding alcohol consumption when taking alcohol-interactive medications. Our results underscore the need for physicians and other health care professionals to discuss the potential risks caused by alcohol–drug interactions with their patients and to monitor the high-risk populations who are elderly, who take multiple medications, or who have medical conditions or other comorbidities. According to the 2011 Behavioral Risk Factor Surveillance System, only 17.4% of current drinkers had ever discussed their alcohol use with a health care professional (McKnight-Eily et al., 2014). Over one third of the surveyed patients with AUD

did not recall being given advice by their primary care providers about avoiding alcohol when taking their medications (Brown et al. 2007). The time constraints of clinician visits have been reported as a barrier to implementing alcohol screening in medical settings, which may be overcome by using technology-based tools (Harris and Knight, 2014). Further improvements in health information technology will also be needed to improve medication safety (Kuperman et al., 2007) as well as bridge the gaps in care coordination and interoperability between the specialists' electronic health records (Samal et al., 2016). These improvements can prevent potential interactions between drugs prescribed by different health care professionals, and increase capabilities of monitoring patients' medical histories and medication uses and side effects over time. With the increase in American prescription drug use as well as the increase in ED visits due to adverse alcohol–drug interaction, it is crucial for health care professionals to ask patients about their alcohol consumption as part of routine examination and warn of any risks of ADR before prescribing and dispensing alcohol-interactive medications (National Institute on Alcohol Abuse and Alcoholism, n.d.).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Trends in estimated incidence of emergency department visits for adverse drug reactions involving alcohol by sex and age group, United States, 2005–2011. [^] $p < 0.05$. APC, annual percent change, based on a joinpoint log-linear regression model weighted by the square of the estimate divided by the variance at each time period.

Table 1

Characteristics and disposition of emergency department visits for adverse drug reactions with alcohol involvement (ADR-A) and without alcohol involvement (ADR-NA)—patients age 12 years and older, United States, 2005–2011.

Characteristics	Total ^d			Males			Females		
	ADR-A (N = 25,303)	ADR-NA (N = 1,741,531)	% (95% CI)	ADR-A (N = 15,057)	ADR-NA (N = 648,793)	% (95% CI)	ADR-A (N = 10,247)	ADR-NA (N = 1,092,738)	% (95% CI)
Sex									
Male	59.5 (56.8–62.3)	37.3 (36.8–37.7)	<i>p</i> < .0001	—	—	—	—	—	—
Female	40.5 (37.7–43.2)	62.7 (62.3–63.2)		—	—	—	—	—	—
Age			<i>p</i> < .0001			<i>p</i> < .0001			<i>p</i> < .0001
12–20	4.9 (3.7–6.0)	7.3 (6.9–7.7)		3.6 (2.3–4.9)	6.6 (6.2–7.1)		6.6 (4.4–8.9)	7.7 (7.3–8.1)	
21–34	23.5 (19.8–27.2)	16.8 (16.1–17.4)		23.9 (19.0–28.9)	14.0 (13.3–14.7)		22.9 (18.9–26.8)	18.4 (17.7–19.1)	
35–54	43.3 (40.4–46.3)	27.2 (26.6–27.8)		43.0 (39.0–47.1)	26.4 (25.5–27.3)		43.8 (39.4–48.2)	27.7 (27.2–28.3)	
55+	28.3 (24.8–31.8)	48.7 (47.5–49.9)		29.4 (25.4–33.3)	52.9 (51.5–54.4)		26.7 (22.2–31.3)	46.2 (45.0–47.4)	
Number of implicated drugs			<i>p</i> = 0.0003			<i>p</i> = 0.24			<i>p</i> = 0.002
1	76.7 (74.4–79.1)	81.0 (80.2–81.9)		77.5 (74.0–81.0)	80.2 (79.1–81.3)		75.6 (72.0–79.2)	81.5 (80.7–82.4)	
2	15.7 (13.7–17.8)	13.3 (12.8–13.7)		16.0 (13.1–18.8)	13.8 (13.2–14.4)		15.4 (12.1–18.6)	13.0 (12.5–13.5)	
3	4.3 (3.1–5.5)	2.9 (2.7–3.1)		3.9 (2.3–5.4)	3.2 (2.9–3.4)		4.9 (2.8–7.0)	2.8 (2.6–3.0)	
4+	3.3 (2.2–4.3)	2.8 (2.3–3.3)		2.7 (1.4–4.0)	2.9 (2.3–3.5)		4.1 (2.4–5.8)	2.7 (2.3–3.2)	
Disposition ^c			<i>p</i> < .0001			<i>p</i> = 0.02			<i>p</i> = 0.003
Less serious outcomes	71.4 (68.3–74.4)	75.7 (74.4–77.1)		70.1 (66.0–74.1)	72.7 (71.2–74.1)		73.3 (69.2–77.3)	77.5 (76.2–78.8)	
More serious outcomes	25.4 (22.5–28.2)	22.6 (21.3–23.9)		26.5 (22.8–30.3)	25.4 (23.9–26.9)		23.6 (19.9–27.4)	20.9 (19.7–22.2)	
All other disposition	3.3 (2.2–4.4)	1.7 (1.3–2.0)		3.4 (2.1–4.7)	1.9 (1.5–2.3)		3.1 (1.4–4.8)	1.5 (1.2–1.8)	

—, not applicable category; CI, confidence interval; N, annual estimated number of ED visits (weighted).

^aED visits without age or sex information were excluded.

^bAll p-values are based on two-tailed Rao-Scott chi-square test.

^cLess serious outcomes included treated and released to home or to police/jail, and referred to detox or another treatment. More serious outcomes included admission to the same hospital, transfer to another medical facility, and death. All other dispositions included left against medical advice, not documented, and other.

Table 2

National annual estimates of emergency department visits for adverse drug reactions with alcohol involvement (ADR-A) and without alcohol involvement (ADR-NA)—stratified by therapeutic medication class of DAWN Drug Reference Vocabulary, sex, and age groups 12 years and older, United States, 2005–2011.

Therapeutic medication class ^a	ADR-A			ADR-NA			<i>b</i> <i>p</i> -value
	N	% (95% CI)	N	% (95% CI)			
Psychotherapeutic agents	All, ages 12+	3,486	13.8 (11.5–16.0)	132,458	7.6 (7.3–8.0)	<.0001	
	Males	2,085	13.8 (10.6–17.1)	49,368	7.6 (7.1–8.1)	<.0001	
	Females	1,401	13.7 (11.0–16.3)	83,090	7.6 (7.3–8.0)	<.0001	
	Ages 12–20	237	19.3 (10.2–28.4)	13,409	10.5 (9.7–11.4)	0.02	
	Ages 21–34	1,014	17.1 (11.6–22.5)	32,629	11.2 (10.6–11.8)	0.01	
	Ages 35–54	1,555	14.2 (11.3–17.1)	45,551	9.6 (9.1–10.1)	0.0002	
	Ages 55+	679	9.5 (4.9–14.0)	40,869	4.8 (4.4–5.2)	0.007	
CNS agents	All, ages 12+	14,954	59.1 (55.8–62.4)	472,335	27.1 (26.4–27.9)	<.0001	
	Males	8,455	56.2 (52.1–60.2)	181,877	28.0 (27.1–29.0)	<.0001	
	Females	6,499	63.4 (58.4–68.4)	290,459	26.6 (25.8–27.3)	<.0001	
	Ages 12–20	718	58.4 (46.0–70.9)	37,540	29.5 (28.2–30.8)	<.0001	
	Ages 21–34	3,744	63.0 (57.1–68.8)	96,098	32.9 (31.7–34.0)	<.0001	
	Ages 35–54	6,892	62.8 (57.5–68.2)	140,401	29.6 (28.5–30.7)	<.0001	
	Ages 55+	3,601	50.3 (44.8–55.8)	198,296	23.4 (22.5–24.3)	<.0001	
Respiratory agents	All, ages 12+	857	3.4 (2.4–4.3)	69,374	4.0 (3.8–4.2)	0.26	
	Males	344	2.3 (1.2–3.4)	24,073	3.7 (3.4–4.1)	0.06	
	Females	513	5.0 (3.2–6.8)	45,300	4.1 (3.9–4.4)	0.30	
	Ages 12–20	88	7.2 (2.3–12.0)	8,182	6.4 (5.8–7.1)	0.76	
	Ages 21–34	174	2.9 (1.6–4.3)	14,360	4.9 (4.5–5.3)	0.03	
	Ages 35–54	332	3.0 (1.4–4.6)	22,115	4.7 (4.3–5.0)	0.10	
	Ages 55+	264	3.7 (1.6–5.8)	24,717	2.9 (2.7–3.2)	0.43	
Cardiovascular agents	All, ages 12+	2,071	8.2 (6.4–9.9)	201,322	11.6 (10.9–12.2)	0.0008	
	Males	1,292	8.6 (6.1–11.0)	83,631	12.9 (12.1–13.7)	0.003	
	Females	779	7.6 (5.3–9.9)	117,692	10.8 (10.2–11.4)	0.02	
	Ages 12–20	—	—	2,252	1.8 (1.4–2.1)	—	

Therapeutic medication class ^a	ADR-A			ADR-NA			<i>p</i> -value ^b
	N	% (95% CI)		N	% (95% CI)		
Anti-infectives	Ages 21–34	128	2.1 (0.3–4.0)	10,925	3.7 (3.3–4.1)		0.20
	Ages 35–54	757	6.9 (4.9–8.9)	44,264	9.3 (8.7–10.0)		0.04
	Ages 55+	1,183	16.5 (12.1–21)	143,882	17.0 (16.0–17.9)		0.84
	All, ages 12+	1,187	4.7 (3.5–5.9)	345,202	19.8 (19.3–20.4)		<.0001
	Males	456	3.0 (1.9–4.1)	100,146	15.4 (14.8–16.1)		<.0001
	Females	732	7.1 (4.8–9.5)	245,056	22.4 (21.8–23.1)		<.0001
	Ages 12–20	87	7.1 (2.1–12.0)	40,940	32.2 (30.8–33.6)		<.0001
	Ages 21–34	403	6.8 (4.2–9.4)	80,125	27.4 (26.4–28.4)		<.0001
	Ages 35–54	432	3.9 (2.0–5.8)	101,132	21.3 (20.6–22.1)		<.0001
	Ages 55+	266	3.7 (2.0–5.4)	123,005	14.5 (13.9–15.2)		<.0001
Coagulation modifiers	All, ages 12+	985	3.9 (2.8–5.0)	174,155	10.0 (9.3–10.7)		<.0001
	Males	704	4.7 (3.1–6.3)	86,180	13.3 (12.3–14.3)		<.0001
	Females	281	2.7 (1.4–4.1)	87,975	8.1 (7.5–8.7)		<.0001
	Ages 12–20	—	—	230	0.2 (0.1–0.3)		—
	Ages 21–34	—	—	3,612	1.2 (0.9–1.5)		—
	Ages 35–54	257	2.3 (1.1–3.6)	21,405	4.5 (4.1–4.9)		0.01
	Ages 55+	668	9.3 (6.3–12.4)	148,907	17.6 (16.4–18.7)		<.0001
	All, ages 12+	649	2.6 (1.5–3.7)	62,625	3.6 (3.3–3.9)		0.12
	Males	355	2.4 (1.0–3.8)	19,760	3.0 (2.7–3.4)		0.40
	Females	294	2.9 (1.1–4.6)	42,865	3.9 (3.6–4.2)		0.33
Gastrointestinal agents	Ages 12–20	—	—	3,344	2.6 (2.1–3.1)		—
	Ages 21–34	—	—	9,472	3.2 (2.9–3.6)		—
	Ages 35–54	191	1.7 (0.8–2.6)	17,108	3.6 (3.2–4.0)		0.005
	Ages 55+	289	4.0 (1.5–6.6)	32,700	3.9 (3.5–4.3)		0.88
	All, ages 12+	680	2.7 (1.2–4.1)	12,227	0.7 (0.6–0.8)		<.0001
	Males	656	4.4 (2.0–6.8)	6,180	1.0 (0.8–1.2)		<.0001
	Females	—	—	6,047	0.6 (0.5–0.6)		—
	Ages 12–20	—	—	809	0.6 (0.5–0.8)		—
	Ages 21–34	—	—	1,817	0.6 (0.5–0.7)		—
	Ages 35–54	—	—	2,742	0.6 (0.5–0.7)		—
Genitourinary-tract agents	Ages 12–20	—	—	2,742	0.6 (0.5–0.7)		—
	Ages 21–34	—	—	2,742	0.6 (0.5–0.7)		—
	Ages 35–54	—	—	2,742	0.6 (0.5–0.7)		—
	All, ages 12+	—	—	2,742	0.6 (0.5–0.7)		—
	Males	—	—	2,742	0.6 (0.5–0.7)		—
	Females	—	—	2,742	0.6 (0.5–0.7)		—
	Ages 12–20	—	—	2,742	0.6 (0.5–0.7)		—
	Ages 21–34	—	—	2,742	0.6 (0.5–0.7)		—
	Ages 35–54	—	—	2,742	0.6 (0.5–0.7)		—
	All, ages 12+	—	—	2,742	0.6 (0.5–0.7)		—

Therapeutic medication class ^a	ADR-A			ADR-NA			<i>p</i> -value ^b
	N	% (95% CI)		N	% (95% CI)		
Hormones	Ages 55+	229	3.2 (1.3–5.1)	6,859	0.8 (0.6–1.0)		<.0001
	All, ages 12+	657	2.6 (1.6–3.6)	92,656	5.3 (5.0–5.6)		0.0002
	Males	319	2.1 (0.7–3.5)	22,306	3.4 (3.1–3.7)		0.14
	Females	338	3.3 (1.7–4.9)	70,350	6.4 (6.1–6.8)		0.004
	Ages 12–20	—	—	10,995	8.6 (7.8–9.5)		—
	Ages 21–34	91	1.5 (0.4–2.6)	23,537	8.1 (7.5–8.7)		<.0001
	Ages 35–54	181	1.6 (0.7–2.6)	25,292	5.3 (4.9–5.8)		<.0001
Metabolic agents	Ages 55+	337	4.7 (1.7–7.7)	32,832	3.9 (3.5–4.2)		0.53
	All, ages 12+	2,052	8.1 (6.4–9.8)	157,192	9.0 (8.3–9.8)		0.24
	Males	1,567	10.4 (8.2–12.6)	72,111	11.1 (10.1–12.2)		0.48
	Females	485	4.7 (3.0–6.5)	85,081	7.8 (7.1–8.4)		0.004
	Ages 12–20	—	—	2,235	1.8 (1.4–2.1)		—
	Ages 21–34	184	3.1 (1.5–4.6)	8,693	3.0 (2.6–3.3)		0.88
	Ages 35–54	860	7.8 (5.6–10.1)	37,551	7.9 (7.2–8.6)		0.94
Nutritional products	Ages 55+	991	13.8 (10.6–17.1)	108,712	12.8 (11.7–14)		0.48
	All, ages 12+	472	1.9 (1.1–2.7)	39,729	2.3 (2.1–2.5)		0.34
	Males	242	1.6 (0.9–2.4)	13,783	2.1 (1.9–2.4)		0.25
	Females	230	2.2 (0.5–4.0)	25,946	2.4 (2.1–2.6)		0.88
	Ages 12–20	—	—	1,459	1.1 (0.8–1.5)		—
	Ages 21–34	68	1.1 (0.2–2.1)	4,982	1.7 (1.5–1.9)		0.35
	Ages 35–54	229	2.1 (0.5–3.7)	10,913	2.3 (2.1–2.5)		0.80
Others ^c	Ages 55+	173	2.4 (1.0–3.8)	22,376	2.6 (2.3–3.0)		0.77
	All, ages 12+	703	2.8 (1.8–3.7)	177,784	10.2 (9.6–10.8)		<.0001
	Males	360	2.4 (1.3–3.5)	65,003	10.0 (9.3–10.7)		<.0001
	Females	343	3.3 (1.6–5.1)	112,781	10.3 (9.7–10.9)		<.0001
	Ages 12–20	—	—	10,476	8.2 (7.2–9.3)		—
	Ages 21–34	138	2.3 (0.5–4.2)	25,844	8.8 (8.3–9.4)		0.0002
	Ages 35–54	285	2.6 (1.2–4.0)	49,204	10.4 (9.7–11)		<.0001
Unknown	Ages 55+	230	3.2 (1.3–5.2)	92,260	10.9 (10.1–11.7)		<.0001
	All, ages 12+	861	3.4 (2.5–4.3)	54,791	3.1 (2.9–3.4)		0.59

Therapeutic medication class ^a	ADR-A		ADR-NA		<i>p</i> -value ^b
	N	% (95% CI)	N	% (95% CI)	
Males	518	3.4 (2.1–4.7)	21,456	3.3 (3.0–3.6)	0.84
Females	343	3.3 (2.2–4.5)	33,335	3.1 (2.8–3.3)	0.62
Ages 12–20	54	4.4 (1.3–7.5)	4,886	3.8 (3.1–4.6)	0.72
Ages 21–34	250	4.2 (2.2–6.2)	10,913	3.7 (3.4–4.1)	0.65
Ages 35–54	393	3.6 (2.0–5.2)	16,304	3.4 (3.1–3.8)	0.86
Ages 55+	164	2.3 (1.0–3.5)	22,689	2.7 (2.4 – 3.0)	0.58

—, imprecise estimate, or not applicable; CI, confidence interval; CNS, central nervous system; DAWN, Drug Abuse Warning Network; N, annual estimated number of ED visits (weighted).

^aBased on the ED standard drug list 2 (SDLED_2) of DAWN Drug Reference Vocabulary.

^bAll *p*-values are based on two-tailed Rao-Scott chi-square test.

^cOthers include alternative medicines, antineoplastics, biologicals, immunological agents, medical gas, miscellaneous agents, plasma expanders, radiologic agents, and topical agents.

Table 3

National annual estimates of emergency department visits for adverse drug reactions with alcohol involvement (ADR-A) and without alcohol involvement (ADR-NA)—stratified by selected psychotherapeutic, CNS, and genitourinary-tract agents; sex; and age groups 12 years and older, United States, 2005–2011.

Therapeutic Medication Class ^a	ADR-A			ADR-NA			<i>b</i> <i>p-value</i>
	N	% (95% CI)	N	% (95% CI)			
Psychotherapeutic agents							
Antidepressants							
All, ages 12+	2,176	8.6 (6.8–10.4)	78,339	4.5 (4.2–4.7)			<.0001
Males	1,213	8.1 (5.3–10.8)	25,274	3.9 (3.6–4.2)			<.0001
Females	963	9.4 (7.2–11.6)	53,065	4.9 (4.6–5.1)			<.0001
Ages 12–20	144	11.8 (4.0–19.5)	6,312	5.0 (4.3–5.6)			0.01
Ages 21–34	677	11.4 (5.7–17.0)	17,702	6.1 (5.6–6.5)			0.01
Ages 35–54	818	7.5 (5.4–9.5)	27,207	5.7 (5.3–6.1)			0.06
Ages 55+	536	7.5 (4.2–10.8)	27,118	3.2 (2.9–3.5)			0.0002
All, ages 12+	1,555	6.1 (4.7–7.5)	64,775	3.7 (3.5–4.0)			<.0001
Males	1,007	6.7 (4.7–8.7)	28,260	4.4 (3.9–4.8)			0.008
Females	548	5.3 (3.5–7.2)	36,516	3.3 (3.1–3.5)			0.007
Ages 12–20	102	8.3 (2.4–14.2)	8,239	6.5 (5.8–7.2)			0.49
Ages 21–34	430	7.2 (3.9–10.6)	17,466	6.0 (5.5–6.5)			0.42
Ages 35–54	860	7.8 (5.7–10.0)	22,295	4.7 (4.3–5.1)			0.0005
Ages 55+	162	2.3 (0.5–4.0)	16,775	2.0 (1.8–2.2)			0.73
CNS agents							
Analgesics							
All, ages 12+	7,174	28.4 (25.8–30.9)	309,761	17.8 (17.2–18.4)			<.0001
Males	4,169	27.7 (23.8–31.6)	118,227	18.2 (17.4–19.0)			<.0001
Females	3,005	29.3 (25.5–33.2)	191,534	17.5 (16.9–18.2)			<.0001
Ages 12–20	353	28.8 (16.5–41.0)	21,654	17.0 (15.8–18.3)			0.03
Ages 21–34	1,744	29.3 (23.6–35.1)	60,708	20.8 (19.8–21.8)			0.002
Ages 35–54	3,009	27.4 (23.5–31.3)	89,942	19.0 (18.2–19.8)			<.0001
Ages 55+	2,068	28.9 (24.5–33.2)	137,457	16.2 (15.5–17.0)			<.0001
All, ages 12+	4,394	17.4 (15.2–19.5)	177,494	10.2 (9.7–10.6)			<.0001
Males	2,630	17.5 (14.1–20.9)	65,521	10.1 (9.5–10.7)			<.0001
Opiates/opioids							

Therapeutic Medication Class ^a	ADR-A			ADR-NA			<i>p</i> -value ^b
	N	% (95% CI)		N	% (95% CI)		
Nonsteroidal anti-inflammatory agents	Females	1,764	17.2 (14.1–20.3)	111,973	10.2 (9.8–10.7)		<.0001
	Ages 12–20	127	10.4 (3.8–16.9)	11,604	9.1 (8.3–10.0)		0.70
	Ages 21–34	1,097	18.4 (13.0–23.9)	35,152	12.0 (11.3–12.8)		0.007
	Ages 35–54	1,936	17.6 (14.6–20.7)	53,077	11.2 (10.5–11.9)		<.0001
	Ages 55+	1,235	17.2 (13.2–21.3)	77,661	9.2 (8.7–9.7)		<.0001
	All, ages 12+	1,416	5.6 (4.4–6.8)	61,247	3.5 (3.3–3.7)		<.0001
	Males	845	5.6 (4.1–7.2)	24,321	3.7 (3.5–4.0)		0.005
	Females	571	5.6 (3.6–7.6)	36,926	3.4 (3.2–3.6)		0.007
	Ages 12–20	93	7.6 (2.8–12.3)	6,213	4.9 (4.2–5.6)		0.19
	Ages 21–34	368	6.2 (3.4–8.9)	14,308	4.9 (4.5–5.3)		0.33
Anticonvulsants	Ages 35–54	530	4.8 (3.3–6.3)	20,836	4.4 (4.1–4.7)		0.55
	Ages 55+	425	5.9 (3.6–8.3)	19,889	2.3 (2.2–2.5)		<.0001
	All, ages 12+	1,273	5.0 (3.9–6.1)	70,181	4.0 (3.7–4.3)		0.06
	Males	769	5.1 (3.6–6.6)	28,054	4.3 (4.0–4.7)		0.29
	Females	504	4.9 (3.4–6.5)	42,127	3.9 (3.6–4.2)		0.14
	Ages 12–20	25	2.1 (0.4–3.8)	4,891	3.8 (3.2–4.5)		0.14
	Ages 21–34	226	3.8 (1.7–5.9)	13,225	4.5 (4.0–5.0)		0.55
	Ages 35–54	671	6.1 (4.3–8.0)	23,824	5.0 (4.5–5.5)		0.21
	Ages 55+	350	4.9 (2.6–7.2)	28,241	3.3 (3.0–3.7)		0.12
	All, ages 12+	6,245	24.7 (21.3–28.0)	75,760	4.4 (4.1–4.6)		<.0001
Anxiolytics, sedatives, and hypnotics	Males	3,086	20.5 (17.3–23.7)	26,895	4.1 (3.8–4.5)		<.0001
	Females	3,159	30.8 (24.8–36.9)	48,865	4.5 (4.2–4.8)		<.0001
	Ages 12–20	252	20.5 (10.4–30.6)	4,540	3.6 (3.0–4.2)		<.0001
	Ages 21–34	1,499	25.2 (18.1–32.3)	13,474	4.6 (4.1–5.1)		<.0001
	Ages 35–54	2,931	26.7 (22.2–31.3)	23,997	5.1 (4.6–5.5)		<.0001
	Ages 55+	1,563	21.8 (17.5–26.2)	33,749	4.0 (3.6–4.3)		<.0001
	All, ages 12+	4,223	16.7 (14.3–19.1)	45,109	2.6 (2.4–2.8)		<.0001
	Males	2,046	13.6 (10.6–16.6)	15,872	2.4 (2.2–2.7)		<.0001
	Females	2,177	21.2 (17.2–25.3)	29,237	2.7 (2.4–2.9)		<.0001
	Ages 12–20	148	12.1 (5.5–18.6)	1,823	1.4 (1.1–1.7)		<.0001
Benzodiazepines							

Therapeutic Medication Class ^a	ADR-A			ADR-NA			<i>p</i> -value ^b
	N	% (95% CI)		N	% (95% CI)		
Barbiturates	Ages 21–34	1,262	21.2 (13.9–28.6)	7,565	2.6 (2.2–3.0)		<.0001
	Ages 35–54	1,808	16.5 (13.1–19.8)	14,898	3.1 (2.8–3.5)		<.0001
	Ages 55+	1,005	14 (10.7–17.3)	20,824	2.5 (2.2–2.7)		<.0001
	All, ages 12+	138	0.5 (0.1–1.0)	1,775	0.1 (0.1–0.1)		<.0001
	Males	—	—	787	0.1 (0.1–0.2)		0.07
	Females	76	0.7 (0.1–1.4)	988	0.1 (0.1–0.1)		<.0001
	Ages 12–20	—	—	—	—		—
	Ages 21–34	—	—	301	0.1 (0.1–0.2)		—
	Ages 35–54	119	1.1 (0.2–2.0)	743	0.2 (0.1–0.2)		<.0001
	Ages 55+	—	—	—	—		—
CNS stimulants	All, ages 12+	834	3.3 (2.3–4.3)	20,909	1.2 (1.1–1.3)		<.0001
	Males	555	3.7 (2.4–5.0)	10,930	1.7 (1.5–1.9)		<.0001
	Females	279	2.7 (1.4–4.1)	9,979	0.9 (0.8–1.0)		<.0001
	Ages 12–20	140	11.4 (4.9–17.9)	5,613	4.4 (3.8–5.1)		0.002
	Ages 21–34	340	5.7 (3.2–8.3)	7,742	2.6 (2.3–3.0)		0.0003
	Ages 35–54	248	2.3 (1.1–3.4)	5,673	1.2 (1.0–1.4)		0.01
	Ages 55+	—	—	1,881	0.2 (0.2–0.3)		—
	All, ages 12+	920	3.6 (2.7–4.6)	21,830	1.3 (1.2–1.4)		<.0001
	Males	414	2.7 (1.7–3.8)	7,409	1.1 (1.0–1.3)		<.0001
	Females	507	4.9 (2.9–7.0)	14,421	1.3 (1.2–1.5)		<.0001
Muscle relaxants	Ages 12–20	—	—	757	0.6 (0.4–0.8)		—
	Ages 21–34	140	2.4 (1.0–3.7)	4,432	1.5 (1.3–1.8)		0.14
	Ages 35–54	586	5.3 (3.4–7.3)	9,043	1.9 (1.7–2.1)		<.0001
	Ages 55+	167	2.3 (0.7–3.9)	7,599	0.9 (0.8–1.0)		0.004
Genitourinary-tract agents	All, ages 12+	655	2.6 (1.1–4.0)	3,971	0.2 (0.2–0.3)		<.0001
	Males	655	4.4 (1.9–6.8)	3,865	0.6 (0.5–0.7)		<.0001
	Females	0	—	—	—		—
	Ages 12–20	0	—	—	—		—
	Ages 21–34	—	—	367	0.1 (0.1–0.2)		—
	Impotence agents	—	—	—	—		—

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Therapeutic Medication Class ^a	ADR-A		ADR-NA		<i>p</i> -value ^b
	N	% (95% CI)	N	% (95% CI)	
Ages 35–54	—	—	1,268	0.3 (0.2–0.3)	—
Ages 55+	213	3.0 (1.1–4.8)	2,321	0.3 (0.2–0.3)	<.0001

—, imprecise estimate, or not applicable; CI, confidence interval; CNS, central nervous system; DAWN, Drug Abuse Warning Network; N, annual estimated number of ED visits (weighted).

^aBased on the ED standard drug list 2 (SDLED_2), standard drug list 3 (SDLED_3), and standard drug list 4 (SDLED_4) of DAWN Drug Reference Vocabulary.

^bAll *p*-values are based on two-tailed Rao-Scott chi-square test.