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Incidence of Adverse Cardiovascular Events in Adults Following Drug Overdose

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Abstract

Objectives—Drug overdose is a leading cause of cardiac arrest and is currently the second leading cause of overall injury-related fatality in the United States. Despite these statistics, the incidence of adverse cardiovascular events (ACVEs) in emergency department (ED) patients following acute drug overdose is unknown. With this study, we address the 2010 American Heart Association Emergency Cardiovascular Care update calling for research to characterize the incidence of in-hospital ACVE following drug overdose.

Methods—This was a prospective cohort study at two tertiary care hospitals over 12 months. Consecutive adult ED patients with acute drug overdose were prospectively followed to hospital discharge. The main outcome was occurrence of in-hospital ACVE, defined as the occurrence of one or more of the following: myocardial injury, shock, ventricular dysrhythmia, and cardiac arrest.

Results—There were 459 ED patients with suspected drug overdose, of whom 274 acute drug overdose qualified and were included for analysis (mean [±SE] age = 40.3 [±1.0] years; 63% male). Hospital course was complicated by ACVE in 16 patients (some had more than one): 12 myocardial injury, three shock, two dysrhythmia, and three cardiac arrest. The incidence of ACVE was 5.8% overall (95% confidence interval [CI] = 3.6% to 9.3%) and 10.7% (95% CI = 6.6% to 16.9%) among inpatient admissions, with all-cause mortality at 0.7% (95% CI = 0.2% to 2.6%).

Conclusions—Based on this study of adult patients with acute drug overdose, ACVE may occur in up to 9.3% overall and up to 16.9% of hospital admissions. Implications for the evaluation and triage of ED patients with acute drug overdose require further study with regard to optimizing interventions to prevent adverse events.

National estimates of drug-related visits to hospital emergency departments (EDs) from the Drug Abuse Warning Network (DAWN) demonstrate a marked increase in drug-related ED visits over the past decade, particularly those involving prescription drug abuse. In 2005,

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DAWN estimated that approximately 1.5 million ED visits were associated with drug misuse or abuse.[1] Roughly 10% of these were suicide attempts, and pharmaceuticals were involved in 93% of cases. Poisoning, or the exposure to any drug or chemical that results in harm, is a leading cause of cardiac arrest in patients over 40 years of age.[2–4] According to published data from the U.S. Centers for Disease Control and Prevention, overall nationwide injury-related mortality increased 5.5% from 1999 to 2004, with poisoning mortality accounting for over 60% of this increase,[4] and even more recent data confirm that mortality from drug overdose continues to rise.[5]

Adverse cardiovascular events (ACVEs) comprise a large portion of the morbidity and mortality in drug overdose emergencies according to the 2009 annual report of the National Poison Data System.[2] Using the Poisoning Severity Scoring system,[6] over 19,000 reported cases are classified each year as “major” or “fatal” poisoning. According to the International Liaison Committee on Resuscitation,[7] in-hospital ACVEs frequently complicates poisoning, and include myocardial injury (by biomarker or electrocardiographic evidence),[8] shock (hypotension or hypoperfusion requiring vasopressors),[9] ventricular dysrhythmias (ventricular tachycardia or fibrillation),[10,11] or cardiac arrest.[12] Proposed mechanisms of toxicity for each type of ACVE are outlined in Table 1.

Currently, estimating the risk of in-hospital ACVE based on data from well-designed clinical studies is not possible. Thus, urgent consultation with a medical toxicologist or the regional poison control center is recommended in drug-related cardiovascular events. Unfortunately, standard guidelines for emergency cardiovascular care may not be optimal in the management of acute poisoning and overdose.[13,14]

Recent guidelines for emergency cardiovascular care, endorsed by the American Heart Association (AHA), call for further research “to document the incidence rates of cardiac events secondary to drug toxicity.”[12] To directly address this call for research, the primary aim of this study was to estimate the incidence of ACVE in ED patients with acute drug overdose as per the above AHA recommendation. Based on decades of clinical experience by the senior study investigators, we expected to find ACVE incidence rates at least one order of magnitude higher than mortality figures, which historically has been observed to be approximately 0.5% in prior cohorts.[15,16] As a secondary hypothesis, we anticipated higher morbidity and mortality rates for overdoses involving males,[15] suicidal ideation,[16] and opioids.[17]

METHODS

Study Design

This prospective cohort study enrolled consecutive adult ED patients with acute drug (medication and illicit) overdose over a 12-month period. The study protocol was approved by the institutional review board for all participating institutions with a waiver of informed consent.

Study Setting and Population

Emergency departments from Bellevue Hospital Center and NYU Medical Center, two urban, tertiary care hospitals, were used for enrollment. Both EDs have combined annual visit volumes in excess of 150,000 and are staffed 24 hours per day with board certified emergency physicians.

Study Protocol

Patients with suspected acute drug overdose were initially screened for inclusion using one of two triggers: 1) consultation with the on-call toxicology fellow carrying a pager 24 hours/day and 7 days a week for both study hospitals or 2) by telephone referral of the case to the regional poison control center with certified specialists in poisoning information available to take calls 24 hours a day and 7 days a week. Reporting of suspected acute poisoning to the poison control center in New York City is mandated by public health law. In addition, it is the standard operating procedure at the study institution for all suspected overdoses to involve toxicology consultation regardless of severity, due to the teaching agenda of the active medical toxicology fellowship program. All eligible patients underwent bedside medical toxicology consultation.

Following screening for eligibility, we applied formal inclusion and exclusion criteria to determine whether patients would be included for data analysis. Inclusion criteria were both of the following: acute presentation (presentation within 24 hours of exposure) and suspected overdose (i.e., illicit drug dose sufficient to cause symptoms or any drug exposure greater than its therapeutic dose). Exclusion criteria were the following: alternative diagnosis (per toxicology consultant, e.g., trauma or infection), chronic presentation (i.e., not acute), nondrug overdose (e.g., plant), dermal or inhalational exposures only, age younger than 18 years, anaphylaxis, subjects with incomplete data (left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital), or do-not-resuscitate orders.

Data collection from the medical chart occurred in accordance with accepted guidelines for valid medical chart abstraction, including training of abstractors and 95% agreement of a random sampling of 10 test charts prior to mass data abstraction.[18] Data included demographics (sex, age), exposure information (timing of exposure, number of exposures, intent, suicidality), toxin identification (detail from HPI, serum drug concentrations if available), initial mental status (the Glasgow Coma Scale [GCS] score, agitation, coma), prior cardiovascular disease (hypertension, diabetes, coronary artery disease, congestive heart failure), and toxicology screens (urine ELISA panel and serum concentration, if any). Blood and urine toxicology screen results sent as routine part of clinical care were recorded in order to confirm exposure. Traditional cardiac biomarkers were measured using Bayer reagents (Bayer Healthcare, Cambridge, MA) on the Bayer Advia Centaur analyzer, and the standard cutoff concentration was used for cardiac troponin I (0–0.09 ng/mL, detection limit 0.01 ng/mL, 10% imprecision, 99th percentile cutoff > 0.1 ng/mL). Subjects without a laboratory evaluation of troponin I were recorded as “missing” in the database to avoid misclassification bias, but for the purposes of ACVE coding the missing value was assumed to be negative. Inpatient rhythm strips in the paper charts of inpatients receiving telemetry monitoring were reviewed to evaluate the “alarmed” segments. Data were abstracted to a deidentified electronic database with password protection.

Subjects were prospectively followed to hospital discharge with data that included electronic medical records, paper medical records, consult records, poison center electronic records, and inpatient telemetry monitoring (if any). The primary outcome was in-hospital ACVE, defined as a composite outcome according to four criteria (see “Outcome Measures”). The poison control center uses a daily follow-up system composed of trained personnel blinded to present study hypotheses, including three to four clinical poisoning specialists, six medical toxicology fellows, and 15 to 20 resident rotators. Information from daily follow-up of all active cases is recorded into an electronic database, which was reviewed for all patients. Additionally, hospital medical record follow-up for all patients was performed by one study investigator trained in medical abstraction (AM) and recorded using standardized data collection forms. Results (from electronic physician notes, laboratory records, radiology

results, and discharge summaries) were prospectively available to the study investigators. Patients discharged from the hospital had no further follow-up.

Altered mental status was defined according to charting of any of the following: GCS < 15, "coma," "agitation," or "altered mental status." Suicidal ingestion was defined according to the treating physician's initial impression and confirmed by psychiatry consultation, with disagreements settled by psychiatry consultation note. Multidrug exposures were defined as exposure to more than one drug of any kind, including two drugs of the same drug class (e.g., exposure to lorazepam and clonazepam counted as two drug exposures but only one drug class).

Outcome Measures

Widely accepted cardiovascular endpoints in poisoning are defined according to the International Liaison Committee on Resuscitation and include myocardial injury, shock, dysrhythmia, and cardiac arrest.[7,19] For this study, in-hospital ACVE was defined as the occurrence of at least one of the following: 1) myocardial injury (troponin > 0.09 ng/mL); 2) shock (hypotension requiring vasopressors); 3) ventricular dysrhythmia (ventricular tachycardia or VT, ventricular fibrillation or VF, torsades des pointes or TdP); and 4) cardiac arrest (loss of pulses requiring chest compressions; see Table 2). ACVE was abstracted based on information from electronic medical records (laboratory results, discharge summary, discharge diagnosis), pharmacy records (dispensed and administered medications), alarmed rhythm strip segments (printed daily as part of routine clinical care for patients admitted to telemetry units), and electronic billing records (diagnosis codes, current procedural terminology codes). These records were reviewed daily for all enrolled patients and recorded using standardized data collection forms.

Data Analysis

We calculated overall ACVE incidence rates by dividing the number of patients with ACVE in the study population by the total number of included drug overdoses. Ninety-five percent confidence intervals (CIs) were calculated using the estimated standard error (SE) method (Wilson procedure). Normality testing of demographic data (e.g., age) was confirmed using the Shapiro-Wilk test. Chi-square (with Fisher's exact tests when appropriate) and t-test were calculated for categorical and continuous variables, respectively, with 5% alpha (two-tailed). Sample size was calculated a priori. Assuming a 15% dichotomous ACVE rate (based on clinical experience of the senior investigators), we calculated the need to enroll 237 patients with 80% power to calculate incidence rates with 95% CI widths of 10%. SPSS version 17.0 (IBM SPSS, Armonk, NY) software was used for computer analysis.

RESULTS

Characteristics of Study Subjects

Over the course of the study period, there were 459 suspected acute drug overdoses, of which 185 were excluded (61 chronic exposures, 50 age <18 years, 49 nondrug, 13 alternative diagnosis, six dermal/inhaled exposures, five insufficient data, one anaphylaxis). Thus, 274 individual subjects were analyzed (mean ± SE age = 40.3 ± 1.0 years, 63% male) with no repeat enrollments. Clinical characteristics of subjects in relation to outcomes are summarized in Table 3. There did not appear to be substantial differences between groups with and without ACVE with regard to classic cardiac risk factors (hypertension, diabetes), prior cardiac disease (coronary artery disease, heart failure), or altered mental status at the time of presentation.

The majority of drug exposures were intentional (79%) and over half (55%) occurred with suicidal intent. Numbers of exposures per subject ranged from one to nine (mean ± SD = 2.17 ± 0.08), and over half of all subjects (59%) presented with multidrug overdoses. The top five drug classes involved were benzodiazepines (21.5%), opioids (19.7%), sympathomimetics (18.2%), acetaminophen (18.2%), and antidepressants (14.6%), and outcomes for each class are summarized in Table 4. Drug exposure confirmation through analytical serum/urine testing was lacking in 31% of patients overall.

Arrival via ambulance occurred in 16%. Disposition from the ED for all 274 subjects was: 140 (51%) admitted, 76 (28%) discharged home, 48 (18%) admitted to psychiatry, and 10 (3.6%) left the hospital against medical advice (five from inpatient unit, five from the ED). All-cause mortality occurred in two patients representing 0.7% (95% CI = 0.2% to 2.6%) of the entire cohort; one death (48-year-old male found down with empty syringe still in arm) occurred in the ED on the day of presentation, and the other death (72-year-old female with multidrug overdose, including tricyclics, acetaminophen, and benzodiazepines) occurred in the intensive care unit after a prolonged hospital course.

Main Results

During the course of the study, 16 of 274 total patients experienced in-hospital ACVE. Of these, there were 12 (4%) patients with myocardial injury, three (1%) with shock, two (1%) with dysrhythmia, and three (1%) with cardiac arrest. The incidence of ACVE for inpatient medical admissions was 10.7% (95% CI = 6.6% to 16.9%), and the overall incidence regardless of initial hospital disposition was 5.8% (95% CI = 3.6% to 9.3%). No patients experienced clinically evident ACVE following medical clearance to a psychiatric unit.

Demographically, overdoses in the study overall more frequently involved males with suicidal intent and multidrug exposure; however, there was no statistical association between ACVE and male sex (ACVE, 95% CI = 51% to 85%; non-ACVE, 95% CI = 54% to 64%; chi-square p = 0.3), suicidal intent (ACVE, 95% CI = 14% to 56%; non-ACVE, 95% CI = 51% to 63%; Fisher's exact test p = 0.1), or multidrug overdose (ACVE, 95% CI = 48% to 89%; non-ACVE, 95% CI = 60% to 71%; Fisher's exact test p = 0.8). The top three most common drug classes associated with occurrence of ACVE were opioids (ACVE, 95% CI = 19% to 61%; non-ACVE, 95% CI = 14% to 24%; chi-square p = 0.1), benzodiazepines (ACVE, 95% CI = 23% to 67%; non-ACVE, 95% CI = 16% to 25%; chi-square p = 0.3), and cocaine (ACVE, 95% CI = 14% to 56%; non-ACVE, 95% CI = 13% to 22%; Fisher's exact test p = 0.2). There was no association between the number of exposures and ACVE (ACVE, 2.0 vs. non-ACVE, 2.18; t-test p = 0.5). Similarly, there was no association between any of the top three most common drug classes (opioids, benzodiazepines, sympathomimetics) with occurrence of ACVE. Drug exposure confirmation through analytical serum and urine testing (in addition to suspicion of overdose) was more commonly ordered as part of clinical care in the ACVE group (93% vs. 67%, p = 0.07). Neither altered mental status (chi-square p = 0.7) at presentation nor prior cardiovascular disease (Fisher's exact test p = 1.0) were associated with inpatient ACVE.

Data Quality Assessment

As a matter of data quality control, we reviewed the first month of data and found 13 ED charts with a diagnosis code mentioning "overdose," all of which (100%) were captured by the protocol, including one subject who was later excluded from the analysis due to an alternative diagnosis. Analysis of the study database during the same time period revealed 17 subjects were actually screened (16 included for analysis, one excluded). Thus, the study protocol captured an additional 25% (n = 4) included patients who did not get charted with any mention of "overdose" in the ED diagnosis codes and thus would have been missed by

retrospective chart review. In addition, to evaluate quality of chart abstraction using inter-rater reliability, 10 charts were chosen at random and evaluated for occurrence of ACVE as a dichotomous variable by a second study investigator with 100% agreement (K = 1.0).

DISCUSSION

Our main results are a higher-than-expected rate of inpatient ACVE following acute drug overdose. Because these results are novel, there are no ACVE comparison statistics from overdose cohorts in past literature; however, the ACVE rate reported in this study (5.8%) is one order of magnitude higher than mortality statistics (~0.5%) from two prior overdose cohorts,[16,20] and this rate approximately doubled (10.7%) if only admitted patients were considered. Based on upper ranges of our calculated CIs, the incidence of ACVE for admitted patients may be as high as 16.9% and when evaluating all patients regardless of initial ED triage, the figure may be as high as 9.3% overall. This finding provides a concerning answer to the recent call "to document the incidence rates of cardiac events secondary to drug toxicity" found in the updated AHA guidelines for emergency cardiovascular care.[12] Adding credibility to our data, however, is that the mortality rate in this study (0.7%, 95% CI = 0.2% to 2.6%) was consistent with mortality statistics from two large prior U.S. data sets (rates of approximately 0.5%)[16,20] and as expected was less than rates seen in resource-poor international settings (as high as 6.5% in one recent large data set), where high-morbidity exposures such as oleander and organophosphates are more typical.[21]

We were unable to reproduce any previous associations with overdose mortality (p = NS for sex,[15] suicidal ideation,[16] and opioid exposures[17]) using our composite ACVE endpoint, which indicates that further research evaluating risk factors in this population is urgently needed to optimize overdose treatment and adverse event prevention. Traditional cardiac risk factors (e.g., hypertension, diabetes) were not predictive in this study, suggesting that we must broaden our search for toxicology-specific "cardiac risk factors." In addition, due to the relative frequency of patients with drug overdoses presenting to the ED with unknown exposures,[1] investigations of clinical prognostic indicators are needed to aid medical decision-making for drug overdose emergencies.

An alternative explanation for the relatively high ACVE rate in this study may have been enrollment of "sicker" cases referred to the toxicology service and nonreferral of "straightforward" cases that could theoretically result in selection bias. However, we doubt that selection bias occurred for several reasons. First, it is the standard operating procedure at the study institution for all suspected overdoses to involve toxicology consultation regardless of severity, due to the teaching agenda of the active medical toxicology fellowship program. In addition, reporting of suspected acute poisoning to the poison center in New York City is mandated by public health law. Furthermore, we evaluated for such a selection bias by reviewing the ED diagnosis codes of patients enrolled during the first month of data collection as a matter of data quality control. We found that no ED charts with a diagnosis code mentioning "overdose" were missed by the protocol. In fact, we found that 25% of captured overdoses enrolled by the protocol did not mention "overdose" in the ED diagnosis code and thus would have been missed by a retrospective chart review. For these reasons, we doubt that selection bias explains the observed results.

This study provides an answer to the AHA's 2010 call for research to characterize ACVE incidence due to drug overdose.[12] Our study found ACVE rates that were similar to cardiovascular complication rates in patients presenting to EDs with acute chest pain; for example, the Multi-center Chest Pain Study[22] estimated this figure at 8.9% (outcomes: 72-hour arrhythmia, shock, ischemia, death). The total number of reported poisonings in the

United States each year (1.5 to 2.5 million)[1,2] is close to the number of acute presentations for chest pain (approximately 5.5 million).[23] Thus, the large volume gap in cardiovascular prediction research between overdose science (medical toxicology) and chest pain science (cardiology), given the findings of the current study, provides sufficient cause for concern.

Our findings regarding the lack of association between mental status and ACVE call into question the medical clearance of overdose patients based solely on normalization of mental status or resolution of coma. A recent study derived electrocardiographic criteria that predict ACVE following acute drug overdose;[19] if validated, such criteria would be more appropriate to medically clear a patient from a cardiovascular perspective. However, we were underpowered to make definitive conclusions regarding the lack of association between mental status and ACVE in our population. Regardless, the implications of this finding do require further study to optimize safe criteria for medical clearance of psychiatric patients with acute drug overdose.

The most common ACVE in our study was myocardial injury, accounting for 75% of the adverse events. Drug toxicity and other toxins may cause myocardial injury through a variety of mechanisms. Based on revised clinical classifications of myocardial infarction, poisoning may cause “Type 2” myocardial infarction due to either decreased myocardial oxygen supply or increased demand.[8] Examples of poison-related mechanisms of myocardial injury include coronary artery vasospasm, hypotension, hypertension, and dysrhythmias. The redefinition of “myocardial infarction” does not include myocardial cell death due to specific myocardial toxins (such as carbon monoxide), and immediate toxicity in the short term may in fact affect long-term prognosis.[24] Thus, we agree with the recently published AHA guidelines stipulating that the approach to patients with symptoms of myocardial injury and a history of drug or toxin exposure should differ in both diagnostic evaluation and therapeutic approach.[12] Future research should address the lack of adequate tools to risk stratify poisoned patients in both the short and the long term.

Unfortunately, prediction of ACVE following drug overdose remains difficult. In the future, medical toxicologists and other emergency health care providers may need to expand beyond the “toxidrome” to go from detection to prediction. The current study was unable to show any relationship between prior cardiovascular medical history (e.g., coronary artery disease, hypertension, diabetes) and ACVE, suggesting that classic “cardiac risk factors” may not allow for risk prediction in poisoning. Therefore, evaluation and triage of ED patients continues to require further study to optimize event prediction. Future cohorts should include robust data collection and sample size to allow for factor analysis to facilitate ACVE prevention.

LIMITATIONS

There are several limitations of this study that require consideration. While the number of ACVE was relatively small and limited statistical power for risk-factor analysis, parallel data collection is ongoing by the study investigators at regional institutions. It is difficult to distinguish between ACVE being the underlying cause for admission versus ACVE occurring unexpectedly after admission; however, both of these are important causes of morbidity, and future studies should evaluate both. Furthermore, while missing troponin data may have led to a slight underestimation of ACVE incidence, it is likely that clinicians did not order the test because it was in fact not indicated (i.e., would be negative if sent). The urban affiliate hospitals in this study represent only one medical school (New York University) and thus may not be generalizable to all settings. Despite the fact that reporting of suspected acute poisoning in New York City is mandated by public health law, one cannot exclude the possibility of referral bias (i.e., underconsultation); however, the data do

represent a sufficiently full spectrum of poisoning severity, as expected. Exposure confirmation through analytical testing was lacking in a subset of patients; however, suspicion of overdose based on history, clinical findings, or ancillary testing was documented by emergency physicians and consulting medical toxicologists. Finally, this study was underpowered to conduct a robust factor analysis, which will require further ongoing study.

CONCLUSIONS

Based on this study of adult patients with acute drug overdose, adverse cardiovascular events may occur in up to 9.3% overall and up to 16.9% of hospital admissions. This study was unable to reproduce previously defined clinical correlates of overdose mortality, despite a relatively high adverse cardiovascular event rate. Thus, future studies should derive novel prognostic models for the evaluation and triage of ED patients with acute drug overdose.

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Table 1

Mechanisms and Pathophysiology of ACVEs Following Drug Overdose

ACVE	Mechanism	Pathophysiology
Myocardial injury	• Decreased myocardial O_2 supply	• Coronary artery vasospasm • Dysrhythmia • Hypotension
	• Increased myocardial O_2 demand	• Hyperthermia/agitation • Dysrhythmia • Hypertension
	• Myocardial cell death	• Low O_2 delivery (e.g., CO) • Inhibition of oxidative phosphorylation
Shock	• Decreased intravascular volume	• Fluid losses • Gastrointestinal hemorrhage
	• Decreased systemic vascular resistance • Diminished myocardial contractility	• Vasodilation • Beta adrenergic blockade • Ca^{2+}/Na^{+} channel blockade • Myocardial stunning
Ventricular dysrhythmia	• Myocardial sensitization	• QT prolongation/dispersion • K^{+} channel blockade
	• Myocardial irritability	• Premature contractions • Intracellular Ca^{2+} release

ACVEs = adverse cardiovascular events; Ca^{2+} = calcium ion; CO = carbon monoxide; K^{+} = potassium ion; Na^{+} = sodium ion; O_2 = oxygen.

Table 2

Definition of ACVEs, According to the International Liaison Committee on Resuscitation[12]

Composite Outcome	Definition
Myocardial injury	Elevation in cardiac troponin I (>0.09 ng/mL)
Shock	Hypotension or hypoperfusion requiring use of a vasopressor
Ventricular dysrhythmia	Ventricular tachycardia/fibrillation or torsades des pointes
Cardiac arrest	Loss of pulses requiring cardiopulmonary resuscitation

ACVEs = adverse cardiovascular events.

Table 3

Clinical Characteristics of Subjects

Clinical Characteristic	Total	ACVE	No ACVE
Age (yr)	40.3 (±1.0)	51.3 (±2.6)	39.5 (±1.0)
Female	102 (37)	4 (25)	98 (38)
Past medical history			
Hypertension	26 (9)	4 (25)	22 (9)
Diabetes	16 (6)	2 (13)	14 (5)
Coronary disease	13 (5)	0 (0)	13 (5)
Heart failure	5 (2)	0 (0)	5 (2)
MS			
Any altered MS	155 (57)	10 (63)	145 (56)
Totals	274	16	258

Values are reported as *n* (%) or mean (±SE).

ACVE = adverse cardiovascular events; MS = mental status; SE = standard error.

Table 4

Most Common Drug Classes Overdosed With Outcomes

Drug Class	Total	ACVE	No ACVE
Benzodiazepines	59	7	52
Opioids	54	6	48
Sympathomimetic	50	5	45
APAP-containing	50	2	48
Antidepressants	40	1	39
Totals[*]	274	16	258

ACVE = adverse cardiovascular events; APAP = acetaminophen.

[*] Not all rows/columns add up, due to multidrug coingestions.