Evolving Epidemiology of Drug-Induced Seizures Reported to a Poison Control Center System

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ABSTRACT

Introduction: We sought to determine whether or not the causes and consequences of drug-induced seizures have changed in the last decade.

Methods: We conducted a retrospective review of all calls to the California Poison Control System in 2003 in which seizures occurred in association with poisoning or drug intoxication. We reviewed the poison center chart of each case to determine the drug(s) involved, the type of seizures, and the medical outcome. We compared the cause of reported seizures to that found in previous investigations.

Results: 386 cases were evaluated and related to poisoning or drug intoxication. The leading causes of seizures were bupropion (89 cases, 23%), diphenhydramine (32 cases, 8.3%), tricyclic antidepressants (30 cases, 7.7%), tramadol (29 cases, 7.5%), amphetamines (27 cases, 6.9%), isoniazid (23 cases, 5.9%), and venlafaxine (23 cases, 5.9%). Since 1993, there was a statistically significant increase in antidepressant related seizures but a decrease in TCA and cocaine related seizures. In 265 patients (68.6%) only a single seizure was reported, while 3.6% (14 cases) reported status epilepticus. Two-thirds (65.5%) of the cases involved suicide attempts and 14.8% the direct result of drug abuse. There were 7 deaths. Of the 7 deaths, 4 people had significant hyperthermia. There was a statistically significant increased risk of death associated with stimulant exposure.

Conclusion: While tricyclic antidepressants, antihistamines, stimulants, and isoniazid remain common causes of drug induced seizures, bupropion, tramadol, and venlafaxine have emerged as common causes of drug-induced seizures for which poison center consultation is requested.

INTRODUCTION

Seizures are a serious complication associated with medication or drug use. Seizures have been associated with hyperthermia, acidosis, anoxic brain injury, and an 8-fold increased risk of aspiration pneumonitis [1]. It is estimated that 6.1% of new onset seizures are drug related [2]. Other studies have determined that up to 9% of cases of status epilepticus presenting to the emergency department may result from drug toxicity [3]. Seizures have been reported to occur following recreational drug use and overdose [4]. Understanding which drugs are most likely associated with seizures may alert clinicians to monitor closely and to treat promptly patients whose poisonings involve the aforementioned substances. Ascertaining the probable clinical course and likelihood for complications related to drug-induced seizures can guide patient disposition decisions, foster cost-effective management, and optimize treatment. A retrospective study 10 years ago

Keywords: drug induced seizures, status epilepticus, seizure morbidity, seizure complications

Notes: This manuscript was previously presented as an abstract in a poster presentation at the North American Congress of Clinical Toxicology in Seattle, 2004.

Acknowledgements: Funding Source: HRSA CFDA 93.253/ Grant: H4BHS00029-05-01

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reported that the leading causes of drug-induced seizures were tricyclic anti-depressants, cocaine, and other stimulants [5]. With the evolving changes in pharmaceutical prescribing patterns as well as the changes in patterns of drugs of abuse, past epidemiological studies may not adequately inform today's clinicians in evaluating patients with drug ingestion. Periodic population-based studies are needed to help clinicians better predict which seizure patients are currently at greater risk for complications and mortality. The purpose of this study is to describe the current trends of drug related seizures reported to a large poison control system. Further, the purpose of this investigation is to identify risk factors associated with mortality from drug-induced seizures.

MATERIALS AND METHODS

Beginning in 2003, we conducted a retrospective review of calls to our statewide poison control system, the California Poison Control System (CPCS), for a 12-month period. The study population included coded cases where seizure was identified as an outcome. Investigators reviewed the poison center chart of each case to determine the drug(s) involved, patient demographics (gender and age), the type and pattern of seizures, clinical data, treatment, and the medical outcome. Status epilepticus was defined as a single seizure lasting greater than 30 minutes or as multiple seizures without full recovery of consciousness. Investigators excluded cases when the seizure was coded as being unrelated to the drug or as a medication exposure. Based on reasonable judgment and available information at the time of presentation, the coding was performed either by the medical director or by a Specialist in Poison Information (SPI). The authors selected 50 cases at random and performed an adverse drug reaction causation analysis using the Naranjo criteria in order to verify coding accuracy [6]. There was 98% agreement between the authors on coding for causality. We excluded cases when the exposures did not occur in humans. If more than one drug or medication was involved in the exposure, the drug with a previously described causal association with seizures was attributed as the most likely causal agent. The study was approved by our university institutional review board prior to obtaining and analyzing the data.

Analysis was carried out using Microsoft Office Excel. In order to evaluate the evolving epidemiology of drug induced seizures, our study compared the data for common causative agents of seizures to a similar study performed 14 years ago [5]. Further analysis was conducted to determine if certain substances were more likely to result in death. For analysis by substance, the substance in question was compared to the total value for all other substances combined. Statistical analysis was performed using chi squared tests to compare proportions between groups.

RESULTS

Of the 529 identified cases associated with a seizure, 386 cases met the inclusion criteria. Eighty one cases of seizures were coded as unrelated, and 62 cases were coded as unknown if related.

Table 1: Demographic information for subjects.

Number of Cases (percentage) **N = 386**	
REASON FOR POISONING	
Suicide	253 (65.5%)
Abuse	57 (14.8%)
Accidental/unintentional	37 (9.6%)
Unknown	39 (10.1%)
AGE	
0–5	27 (7.0%)
6–12	9 (2.3%)
13–18	74 (19.2%)
> 18	276 (71.5%)
DESCRIPTION OF SEIZURE	
Single	265 (68.6%)
Two or more	107 (27.7%)
Status epilepticus	14 (3.6%)

This information compares the data to the 1993 study that demonstrated drug related seizures: causes - *46.1% suicide, 19.9% abuse, 21.5% unintentional, 12.6% unknown;* ages – *9.4% < 12years, 76% adolescent/adult, 7.3% >60 years, 7.3% unknown;* description- *61.7% brief, prolonged 21.5%, unknown 16.8% [5].*

Table 1 describes the demographics of the study population. Two hundred fifty three cases of seizures occurred as a result of an attempted suicide, and a majority of the seizures occurred in adults. In 265 patients (68.6%) only a single seizure was reported, while 27.7% (107 cases) reported 2 or more discrete seizures, and 3.6% (14 cases) reported status epilepticus. There was not a clear pattern to which patients developed status epilepticus, and some cases may have resulted from secondary effects (such as cerebral edema, severe acidosis, and other effect) or co-ingestants. The substance exposures that were associated with status epilepticus include benzonatate, cocaine, bupropion, ethylene glycol, isoniazid, citalopram, amitriptyline, methamphetamine, and tiagabine. There were 7 deaths.

The leading causes of seizures (*Figure 1*) were bupropion (89 cases, 23%), diphenhydramine (32 cases, 8.3%), tricyclic antidepressants (30 cases, 7.7%), tramadol (29 cases, 7.5%), amphetamines (27 cases, 6.9%), isoniazid (23 cases, 5.9%), and venlafaxine (23 cases, 5.9%). Of the remaining causes, various classes of antipsychotics (18 cases, 4.7%), MDMA (13 cases, 3.4%), cocaine (19 cases, 4.9%), and other antidepressants (excluding bupropion and TCAs) (36 cases, 9.3 %) comprised a large portion. The remainder of the seizures (47 cases, 12.2%) were caused by a wide variety of substances; including, naproxen, ditropan, cogentin, lighter fluid, camphor, glyburide, carbon monoxide, lamotrigine, meperidine, phenytoin, ethylene glycol, lindane, baclofen, propoxyphene, tiagibine, dicyclomine, thorazine, methyl phenidate, methyl bromide, lithium, lidocaine, cyproheptadine, bupivicaine, acetyl salicylic acid, valproic acid, oxcarbazepine, chlorpromazine, and glipizide. More than one epileptogenic drug was involved in 71 (18.4%) cases.

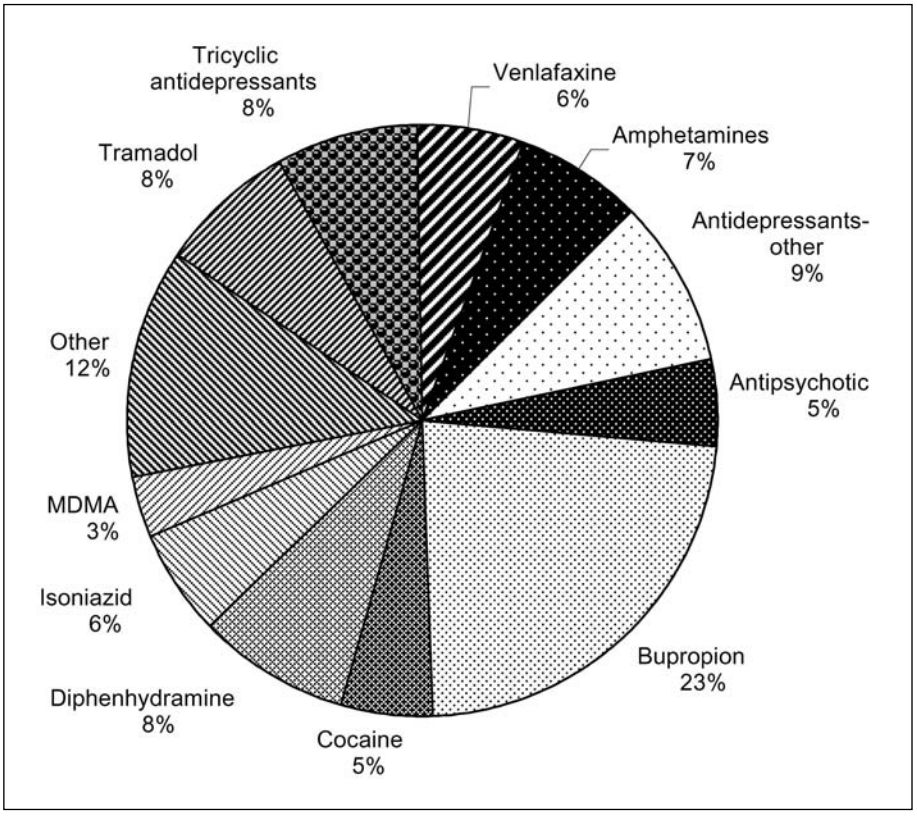

Figure 1: Breakdown of Seizures by Drug Type.

Table 2 demonstrates the changes in epidemiology of drug induced seizures reported to the poison control center. Compared to the 1993 study, this data reveals that there was a statistically significant decrease in seizures caused by tricyclic antidepressants (TCA) (OR = 0.26 [0.16–0.41; 95% CI]) even though there was an overall increase in antidepressant induced seizures (OR = 2.12 [1.46–3.06; 95%CI]). Further, the percentage of cases of seizures associated with stimulants showed a decreasing trend (OR = 0.45 [0.3–0.67; 95% CI]), and this trend was most pronounced for cocaine-induced seizures (OR = 0.18 [0.11–0.31; 95% CI]). There was no statistically significant change in the number of reported seizures caused by isoniazid, diphenhydramine, or sedative withdrawal. In our study, there were no reported seizures caused by theophylline, a marked contrast to the previous report.

Table 2: Seizure Causes Compared to Data from Previous Decade

Drug Type	1993: No. Cases (percent)	2003: No. Cases (percent)	OR (95% CI)
Antidepressants (all types)	55 (28.8%)	178 (41.9%)	2.12 (1.46–3.06) $p < 0.001$
Tricyclic antidepressants (TCAs)	47 (24.6%)	30 (7.7%)	0.26 (0.16–0.41) $p < 0.001$
Stimulants	55 (28.8)	59 (15.2)	0.45 (0.3–0.67) $p < 0.001$
Amphetamines	6 (3.1)	27 (6.9)	2.32 (0.96–5.58) $p = 0.061$
Cocaine	42 (21.9)	19 (4.9)	0.18 (0.11–0.31) $p < 0.001$
Diphenhydramine	14 (7.3)	32 (8.3)	1.14 (0.59–2.20) $p = 0.69$
Theophylline	10 (5.2)	0	NA
Isoniazid	10 (5.2)	23 (5.9)	1.14 (0.53–2.46) $p = 0.725$
Sedative withdrawal	5 (2.6)	8 (2.1)	0.79 (0.25–2.43) p=0.678
TOTAL	191	386	

Table 3: Description of Deaths Associated with Drug Related Seizures

Case Number	Age/Gender	Substance	Hyperthermia	Body Stuffer	Reason for exposure
1	40 y/o Female	Amitryptiline	No;	No	Suicide
			T=93.7		
2	43 y/o male	Bupropion	Yes;	No	Suicide
			T=103		
3	23 y/o male	MDMA and methamphetamine	Yes;	No	Abuse
			T=105		
4	23 y/o female	Cocaine	Yes;	Yes	Abuse
			T=103		
5	44 y/o male	Methamphetamine	Yes;	Yes	Abuse
			T=104		
6	52 y/o male	Bupropion and aspirin	No temp documented	No	Suicide
7	26 y/o male	Venlafaxine and diltiazem	No temp documented	No	Suicide

Table 3 describes the characteristics of the 7 patients who died. Five of the patients were male. Three of the patient exposures resulted from abuse, 2 of whom (in order to avoid arrest) engaged in body stuffing substances. Only 5 of the cases had documented temperatures, and in 4 cases severe hyperthermia (temp > 103 F) was reported. Of the 7 fatal cases involving drug induced seizures, 3 were related to stimulant exposures. This finding (*Table 4*) was statistically significant when compared to all other causes of death (RR = 4.31 [1.06–17.55; 95% CI]). No other drugs associated with death demonstrated a statistically significant trend.

DISCUSSION

This study describes significant, evolving trends in the epidemiology of drug induced seizures reported to a large poison control system. Compared to a prior study of drug-induced seizures in this same region, there are notable and statistically significant changes [5]. While cases involving tricyclic antidepressants, cocaine, and theophylline have shown a marked decrease, newer causes of drug induced seizures have emerged; including: bupropion, tramadol, and venlafaxine. Despite the decreasing trend of TCA induced seizures (OR = 0.26), the overall incidence of antidepressant induced seizures has increased (OR = 1.78). Our data suggests that this finding may be related to the large increase in bupropion induced seizures. This finding is consistent with current reports in the literature [2]. Additionally, therapeutic options for the treatment of depression have markedly increased over the decade while tricyclic antidepressants are often used for alternative indications (such as neuropathic pain) and in lower doses.

Another note worthy trend involves the overall decreasing trend of stimulant related seizures but an increasing number of methamphetamine and MDMA related seizures. In the 1993 study, there were no seizures identified as being caused by MDMA, and amphetamines caused only 6 seizures [5]. Based on other epidemiologic surveys, this increase has been paralleled by an increase in amphetamine and MDMA related ED visits of nearly 114% and 1491%, respectively, from 1994-2002 [7]. Previous studies have shown that seizures due to stimulants, cocaine, and antihistamines were usually brief and self limited while seizures due to tricyclic antidepressants and iso-

Table 4: Odds Ratio for Mortality Based on Substance Ingested

Susbstance	Deaths	Total Exposures to Substance	OR of mortality compared to all other substances
Stimulants	3	59	4.31 (1.06–17.55); p = 0.041
TCAs	1	30	1.94 (0.24–16.06); p = 0.537
Bupropion	2	89	1.34 (0.26–7.0); p = 0.727
Venlafaxine	1	23	2.70 (0.34–21.57); p = 0.348
TOTAL DEATHS	7	386	

niazid were more likely to be multiple and prolonged [5]. However, we found that three of the 7 deaths occurred in patients who had abused stimulants, 2 of whom developed multiple seizures or status epilepticus. While the overall mortality from seizures was low, death was more likely to occur in patients who were exposed to stimulants (RR = 4.31 [1.06–17.55; 95% CI]). Hyperthermia is a recognized complication of prolonged seizures and previous studies have also demonstrated poor outcomes for drug related hyperthermia [8,9]. It is unclear, based on current data, whether hyperthermia is an independent cause of mortality or merely a marker for prolonged seizure. Nevertheless, this association between hyperthermia and death may be a valuable indicator for clinical management.

This study has some limitations. Due to the retrospective nature of the study design, robust data collection and causal assessments are not possible. Second, the generalizability of this study may be limited. Our data reflect the trends occurring in the state of California for 2003 and may not be applicable to the entire country. However, epidemiologic evidence from the Drug Abuse Warning Network (DAWN) publications has suggested that these trends are congruent in respect to the national trends of ED visits [7]. Although our comparisons to previous studies involve regionally acquired data from the same state, we obtained statewide data; the previous investigation derived its data solely from the San Francisco Bay area [5]. It is possible that the change in trends may only reflect differences between a regional and state level. Finally, there is an inherent reporting bias for cases analyzed at our poison control center. Clinicians in regional hospitals report data to the poison control center. The decreasing trends of cocaine induced seizures may be a reflection of clinicians' increasing expertise and comfort in managing this specific exposure; the increasing incidence of bupropion induced seizures may only reflect the unfamiliarity created by the increasing patterns of usage. There is some evidence, however, to contradict the possibility of unfamiliarity. Our study demonstrated no significant changes in the relative frequency of reports of seizures related to isoniazid, diphenhydramine, and sedative withdrawal—three drug related seizures that have had no significant changes in management over the past decade.

The etiology of drug related seizures reported to a large regional poison control center has changed over the past decade. Newer drugs (such as bupropion, tramadol and venlafaxine) accounted for a large proportion of drug-induced seizures, suggesting either increased use of these drugs, less familiarity with these drugs by community physicians, or both. Stimulant drugs were involved in 3 of the 7 fatal cases. Hyperthermia was present in 4 of the 7 patients who died. These findings are useful to the clinician, poison control center staff, and public health personnel—all of whom must keep constant vigilance, provide accurate information, and play a vital role in the prevention of drug related complications.

The authors have no potential conflicts of interest to report.

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