Comparing Acute Toxicity of First- and Second-Generation Antipsychotic Drugs: A 10-Year, Retrospective Cohort Study

Michael A. Ciranni, M.D., Ph.D.;
Thomas E. Kearney, Pharm.D.; and Kent R. Olson, M.D.

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Corresponding author and reprints: Michael Ciranni, M.D., Ph.D., Department of Psychiatry, New York University, 462 1st Ave., NBV 20N11, New York, NY 10016 (e-mail: Michael.ciranni@nyumc.org).

Objective: Second-generation antipsychotics (SGAs) are far more commonly used in the United States compared to first-generation antipsychotics (FGAs), but the relative safety of SGAs compared to FGAs following acute toxic ingestions has not been studied.

Method: A retrospective cohort study was performed by chart review of the California Poison Control System electronic database of 1975 cases from the 10-year period 1997 to 2006 involving patients aged 18 to 65 years who ingested a single SGA or FGA. Cases were coded for overall severity of adverse outcome as defined by the American Association of Poison Control Centers criteria and for presence of specific symptoms and treatments. Odds ratios were calculated between SGAs and FGAs for various symptoms, treatments, and outcome severity.

Results: Odds of a major adverse outcome or death were significantly higher for SGAs than FGAs (OR = 1.71, 95% CI = 1.09 to 2.71). Patients taking SGAs had higher odds of respiratory depression (OR = 2.39, 95% CI = 1.09 to 5.26), coma (OR = 2.18, 95% CI = 1.30 to 3.65), and hypotension (OR = 1.80, 95% CI = 1.23 to 2.63) compared to those taking FGAs but lower odds of dystonia (OR = 0.12, 95% CI = 0.08 to 0.19) or rigidity (OR = 0.30, 95% CI = 0.10 to 0.90).

Conclusion: SGAs appear no safer than FGAs in acute overdose. While neuromuscular symptoms appear less frequently with SGAs compared to FGAs, the relatively greater rates of central nervous system depression associated with SGA overdose may be more dangerous.

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Pharmacologic treatment of schizophrenia in the United States is largely dominated by the use of "atypical," or second-generation, antipsychotics (SGAs), which now comprise 90% of the market share for antipsychotic drugs in the United States.[1] The increased use of SGAs over "typical," or first-generation, antipsychotics (FGAs), has been driven mainly by initial reports of the superior efficacy of SGAs[2,3] as well as their seemingly more benign side effect profile.[4] Compared to FGAs, whose D_2 receptor antagonism reduced psychotic positive symptoms but led to increased extrapyramidal signs and tardive dyskinesia,[5] the SGAs have lower D_2 receptor affinity but greater affinity for serotonin and norepinephrine receptors.[6] This difference in receptor affinities may account for the reduced incidence of extrapyramidal symptoms observed with SGA use, as well as their reputed efficacy in treating negative and cognitive symptoms of schizophrenia.[6]

However, recent studies have questioned the superior efficacy of SGAs over FGAs,[1,7] leading to a reappraisal of SGA use. Long-term use of SGAs may lead to lower rates of extrapyramidal symptoms compared to the FGAs,[8] but this risk appears to have been replaced by a greater tendency toward weight gain[9] as well as altered glucose[10] and lipid metabolism.[11] The relative safety of SGAs compared to FGAs in acute toxic ingestions has not been well studied. Most of the available data on SGA toxicity are based on case reports or case series involving individual SGAs,[8] preventing adequate comparison. Given that the lifetime risk for suicide among persons with schizophrenia is approximately 50% for suicide attempts and 10% for completed suicides,[12] the relative safety of SGAs compared to FGAs warrants further consideration.

The primary goal of this study was to compare the effects of SGAs and FGAs after acute toxic ingestion in a large number of adults as reported to a statewide regional poison control system in terms of symptoms, treatments, and overall severity of outcome. A secondary goal of this study was to examine the frequency with which specific symptoms and treatments were associated with specific SGAs or FGAs.

METHOD

Study Design and Case Selection

A retrospective cohort study was performed by chart review of the California Poison Control System (CPCS) electronic database for cases from the years 1997 through 2006. The CPCS provides treatment advice and referral assistance to the public and to health professionals through its toll-free emergency hotline 24 hours a day, 365 days a year, through 4 highly integrated sites operating under a single administration. Each reported poisoning case is entered prospectively into a clinical database (Visual Dotlab) by trained poison center specialists. The specialists are licensed as either a pharmacist or nurse with special training in clinical toxicology through a regional poison center. They are individually certified by the American Association of Poison Control Centers after passing a standardized national examination. In 2006 alone, the California Poison Control System consulted on 221,798 human poisoning exposure cases that were recorded in its case database.

The poison center specialists enter the initial and follow-up notes into a text field for individuals referred to a health care facility, and for each case enter specific symptom, treatment, and outcome codes according to American Association of Poison Control Centers (AAPCC) criteria.[13,14] Symptom and treatment codes are self-explanatory. Formal definition of the outcome codes is provided by the AAPCC.[13] In general, a minor effect is defined as having "symptoms that were minimally bothersome to the patient and resolve rapidly. The patient returned to a pre-exposure state of well being and had no residual disability or disfigurement."[13(p812)] A moderate effect is defined as having "symptoms which are more pronounced, more prolonged or more of a systemic nature than minor symptoms, but were not life-threatening and the patient had returned to a pre-exposure state of well-being with no residual disability or disfigurement."[13(p813)] A major effect is defined as having "symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement."[13(p813)]

Eligible cases involved adults aged 18 to 65 years with a reported ingestion of an FGA or an SGA who were referred to a health care facility for evaluation and treatment. Table 1 shows the FGAs and SGAs included in our database search. Cases were excluded if they did not receive treatment at a health care facility (e.g., were referred to a facility but never arrived or left against medical advice), if they involved a co-ingestion of another prescription drug, if they involved a co-ingestion of alcohol or a controlled substance, or if no definite outcome was recorded.

Table 1. First- and Second-Generation Antipsychotic Drugs Included in Search

First Generation	Second Generation
Benperidol	Amisulpride
Chlorpromazine	Aripiprazole
Chlorprothixene	Clozapine
Flupenthixol	Melperone
Fluphenazine	Olanzapine
Haloperidol	Quetiapine
Levomepromazine	Risperidone
Molindone	Sertindole
Mesoridazine	Sulpiride
Perphenazine	Ziprasidone
Pimozide	Zotepine
Prothipendyl	
Thioridazine	
Thiothixene	
Trifluoperazine	
Trifluopromazine	
Zuclopenthixol	

Coding of Symptoms, Treatments, and Adverse Outcomes

Data regarding all symptoms, treatments, and outcomes were extracted from the codes assigned to the cases by the poison center specialists as described above, with the exceptions of QT prolongation, wide QRS intervals, and neuroleptic malignant syndrome (NMS), for which there are no specific AAPCC codes. For QT prolongation and wide QRS intervals, one of the authors (M.A.C.) reviewed the text fields of the cases for the necessary information to define these conditions as present or absent using a priori definitions described below.

We classified a case as having a prolonged QT if a recorded QTc was greater than 430 milliseconds in men or 450 milliseconds in women.[15] If there was no QTc recorded but the QT and heart rate were recorded, we used Bazett's formula to calculate the QTc.[16] We also defined a case as having QT prolongation if the text field specifically mentioned a "prolonged" or "abnormal" QT. "Borderline" QTs were not included. Similarly, we classified a case as having a wide QRS if a QRS greater than 120 milliseconds was recorded,[17] if the text field specifically mentioned a "wide" or "abnormal" QRS, or if any kind of ventricular tachycardia was present. Text fields that did not include any QRS or QT information or any mention of an abnormal ventricular rhythm were assumed to have no QRS or QT abnormalities.

To find potential NMS cases, we focused our examination on cases in which fever, dystonia, rigidity, or rhabdomyolysis had already been coded in the database

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as a symptom. We classified the potential NMS cases as being a "possible," "likely," or "unlikely" NMS case using criteria adapted from the research definitions from the DSM-IV-TR.[18] To qualify as a possible NMS case, the text field of a potential case had to specifically mention (1) stiffness or rigidity described concurrently with (2) an elevated temperature, either with text or with a recorded temperature greater than 38ºC or 100.4ºF. Cases that described elevated temperature without concurrent rigidity or stiffness, or vice versa, were classified as unlikely NMS cases. The possible NMS cases were upgraded to likely NMS if (1) the text field described 2 of the 10 possible additional symptoms as defined by criterion B of the DSM-IV research definition of NMS,[15] i.e., diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, or laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase) and (2) there was no alternative diagnosis that was as or more likely to explain the fever and other associated findings. The cases that were not potential NMS cases (i.e., did not have fever, dystonia, rigidity, or rhabdomyolysis as one of the assigned symptom codes) were all classified a priori as unlikely NMS cases without further review. Two of the authors (M.A.C. and K.R.O.) independently classified all the potential NMS cases. Cases that had discrepancies in classification between the first 2 authors were resolved by the third author's (T.E.K.) independent review and classification of the case.

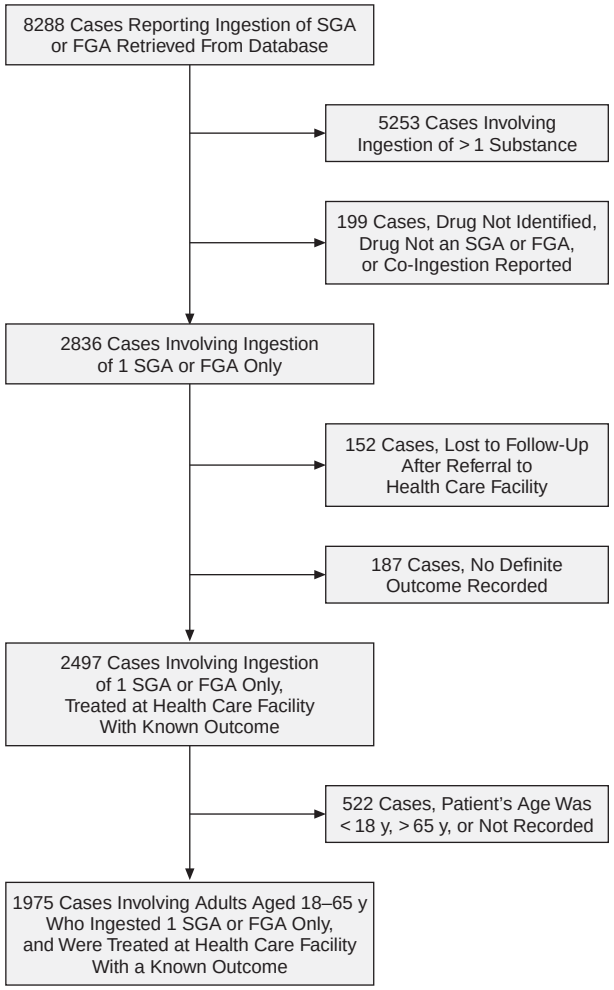
To find potential serotonin syndrome cases, we focused our evaluation on all the potential NMS cases using the symptom coding criteria above, and all cases in which tremor had already been coded as a symptom in the database. We evaluated the clinical information provided in the text field of a potential serotonin syndrome case and applied the Hunter Serotonin Toxicity Criteria decision rules[19] to these potential cases in order to classify them as cases of serotonin syndrome or not. Two of the authors (M.A.C. and K.R.O.) reviewed the potential cases and applied the decision rules independently, with discrepant classifications resolved by the third author's (T.E.K.) independent review and classification of the case.

RESULTS

Selection of Cases for Analysis

Figure 1 shows the selection process for cases that would ultimately be examined in this study. Initially extracted from the database were 8288 cases involving people who had ingested an antipsychotic (FGA or SGA) and were referred to a health care facility. Of those initial cases, 5253 cases involved ingestion of more than 1 substance and were excluded from further analysis. Of the remaining cases, 199 were removed if, on further review, the target drug was not an FGA or SGA, the target drug could not be specifically identified, or a co-ingestion was identified. Another 152 cases were eliminated in which the patient was lost to follow-up after referral to a health care facility. An additional 187 cases were excluded from analysis because no definite outcome of the case was recorded. Finally, 522 cases were excluded in which the patient's age fell outside the 18 to 65 year range or was not recorded, leaving 1975 cases for analysis. Of these, 936 cases (47.4%) were male, 1038 cases (52.6%) were female, and 1 case did not have a record of the gender. The proportion of males to females was not significantly different between FGAs and SGAs ($\chi^2 = 0.312$, df = 1). The mean age for males was 34.3 years, with a standard deviation (SD) of 11.1 years, and the mean age for females was 35.4 years, with an SD of 11.1 years. This difference in age between the sexes was significant ($F = 4.61$, df = 1,1970; $p < .05$); however, there were no overall differences in age between cases of FGA or SGA

Figure 1. Selection of Cases for Analysis



Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

Table 2. Frequency (and percentage) of Adverse Outcomes and Deaths Associated With Second-Generation Antipsychotic (SGA) and First-Generation Antipsychotic (FGA) Use, N (%)

Adverse Outcome	SGA, N = 1568	FGA, N = 407
Minor adverse effect	716 (45.7)	197 (48.4)
Moderate adverse effect	706 (45.0)	187 (46.0)
Major adverse effect	143 (9.1)	23 (5.7)
Death	3 (0.2)	0 (0.0)

ingestion (F = 0.469, df = 1,1970), and the interaction of sex and type of drug ingested on age was not significant (F = 0.305, df = 1,1970). Other demographic information was not recorded.

Frequencies and Odds Ratios Between SGAs and FGAs for Adverse Outcomes

Table 2 shows the numbers of minor, moderate, or major adverse outcomes and deaths associated with SGA or FGA use, as well as the percentage of FGA or SGA cases involving that outcome. The odds of a major adverse outcome or death were significantly greater for the SGA cases (OR = 1.71, 95% CI = 1.09 to 2.71), as shown in the bottom row of Table 3. Of the 143 cases involving major adverse outcomes with SGAs, the most commonly associated symptoms were coma (75 cases), respiratory depression (31 cases), and seizures (11 cases). Of the 23 cases involving major adverse outcomes with FGAs, the most commonly associated symptoms were coma (11 cases), cardiac conduction disturbances (9 cases collectively), and possible or likely NMS (3 and 2 cases, respectively, or 5 cases overall). The 3 deaths reported all involved SGA ingestions, specifically quetiapine. One of the 3 deaths on autopsy appeared to be the result of an intracranial hemorrhage, not drug overdose (although no serum drug levels were obtained). The other 2 patients died of pulmonary complications secondary to aspiration pneumonia.

Frequencies and Odds Ratios Between SGAs and FGAs for Specific Symptoms and Treatments

Table 3 also shows the numbers of occurrences of each symptom or treatment for the FGAs and SGAs overall, as well as the percentage of FGA or SGA cases involving that symptom or treatment. The last column of the table shows the odds ratio and 95% confidence interval of each symptom or treatment occurring with an SGA. An OR with a 95% CI greater than 1 indicates the symptom or treatment was significantly more likely to occur with an SGA than with an FGA, whereas a 95% CI less than 1 indicates the symptom or treatment was significantly less likely to occur with an SGA compared to an FGA. For patients with SGA ingestions, there were significantly greater odds of developing respiratory depression (OR = 2.39, 95% CI = 1.09 to 5.26), coma (OR = 2.18, 95% CI = 1.30 to 3.65), or hypotension (OR = 1.80, 95% CI = 1.23 to 2.63) compared to those with FGA ingestions. In contrast, patients with FGA ingestions had significantly greater odds of developing dystonia (OR = 0.12, 95% CI = 0.08 to 0.19) or rigidity (OR = 0.30, 95% CI = 0.10 to 0.90) compared to those with SGA ingestions. The odds of rhabdomyolysis, fever, or seizure were not significantly different between patients taking SGAs and FGAs.

Only 249 cases (12.6%) had QT information available for analysis, and only 372 cases (18.9%) had QRS information reported. Using the assumption that cases with no QRS or QT information reported did not have any abnormalities, we did not find significantly different odds of developing a wide QRS or prolonged QT between SGAs and FGAs.

There were 245 cases that met criteria to be a potential NMS case and given further review. There was good agreement between the first 2 raters (99.2%, $\kappa = 0.89$) for the classification of potential NMS cases. Of the 245 cases, we found 4 likely and 0 possible NMS cases for the SGAs and 2 likely and 3 possible NMS cases for the FGAs. With the possible and likely NMS cases pooled together, the odds of showing symptoms concerning for NMS were significantly more likely with the FGAs than with the SGAs (OR = 0.21, 95% CI = 0.05 to 0.77). If the analysis was restricted to only the likely NMS cases, there were no differences in frequency of NMS between FGAs and SGAs (OR = 0.52, 95% CI = 0.09 to 2.84).

There were 267 cases that were given further review as potential serotonin syndrome cases. Agreement between the first 2 reviewers was 100% for the application of the Hunter Serotonin Toxicity Criteria. None of the cases reviewed met criteria as a serotonin syndrome case.

In terms of medical interventions used, SGA ingestions had significantly higher odds of involving intubation for airway protection during treatment (OR = 2.49, 95% CI = 1.69 to 3.86) as well as mechanical ventilation for respiratory compromise (OR = 2.79, 95% CI = 1.56 to 4.98). The odds of intravenous (IV) fluid use were significantly higher for the SGA cases (OR = 1.88, 95% CI = 1.44 to 2.46), but odds of vasopressor use did not differ between SGA and FGA cases.

Frequency of Specific Symptoms, Treatments, and Outcomes by Medication

Table 4 shows the number of cases involving each specific SGA or FGA included in the study. The most common SGAs reported in the study were quetiapine (939 cases), olanzapine (333 cases), and risperidone (220 cases), comprising 60%, 21%, and 14%, respectively, of the total SGA sample of 1568 cases. The most common FGAs reported in the study were chlorpromazine (117 cases), haloperidol (99 cases), and thioridazine (82 cases), comprising 29%, 24%, and 20%, respectively, of the total

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Table 3. Odds Ratios for Specific Symptoms, Treatments, and Outcomes Associated With Second-Generation Antipsychotic (SGA) and First-Generation Antipsychotic (FGA) Use

Variable	SGA (N = 1569), N (%)	FGA (N = 407), N (%)	Odds Ratio (95% CI)
Respiratory depression	63 (4.0)	7 (1.7)	2.39 (1.09 to 5.26)
Coma	136 (8.7)	17 (4.2)	2.18 (1.30 to 3.65)
Hypotension	221 (14.1)	34 (8.4)	1.80 (1.23 to 2.63)
Long QT interval	73 (4.7)	28 (6.9)	0.66 (0.42 to 1.04)
Wide QRS interval	21 (1.3)	8 (2.0)	0.68 (0.30 to 1.54)
Dystonia	39 (2.5)	69 (17.0)	0.12 (0.08 to 0.19)
Rigidity	7 (0.5)	6 (1.5)	0.30 (0.10 to 0.90)
Rhabdomyolysis	8 (0.5)	3 (0.7)	0.69 (0.18 to 2.61)
Fever	13 (0.8)	6 (1.5)	0.56 (0.21 to 1.48)
Possible or likely NMS	4 (0.3)	5 (1.2)	0.21 (0.05 to 0.77)
Seizure	30 (1.9)	4 (1.0)	1.97 (0.69 to 5.61)
Intubation	212 (13.5)	24 (5.9)	2.49 (1.69 to 3.86)
Ventilation	132 (8.4)	13 (3.2)	2.79 (1.56 to 4.98)
Intravenous fluids	500 (31.9)	81 (19.9)	1.88 (1.44 to 2.46)
Vasopressors	25 (1.5)	5 (1.2)	1.30 (0.50 to 3.42)
Major adverse outcome or death	146 (9.3)	23 (5.7)	1.71 (1.09 to 2.71)

Abbreviation: NMS = neuroleptic malignant syndrome.

FGA sample of 407 cases. The 2 zuclopenthixol cases were the only cases in our study that involved an antipsychotic not commercially available in the United States. For each SGA or FGA, Table 4 also shows the number and percentage of cases involving that specific SGA or FGA in which a particular symptom or treatment was associated with it. For the 3 most frequently occurring SGAs, the 2 most commonly reported symptoms were as follows: quetiapine, hypotension (165 cases, 17.6%) and coma (96 cases, 10.2%); olanzapine, coma (34 cases, 10.2%) and hypotension (21 cases, 6.3%); and risperidone, hypotension (29 cases, 13.2%) and dystonia (19 cases, 8.6%). For the 3 most frequently occurring FGAs, the 2 most commonly reported symptoms were as follows: chlorpromazine, hypotension (10 cases, 8.6%) and coma (8 cases, 6.8%); haloperidol, dystonia (39 cases, 39.4%) and hypotension (8 cases, 8.1%); and thioridazine, long QT (14 cases, 17.1%) and hypotension (10 cases, 12.2%). Direct comparison of symptom percentages between individual drugs is limited by the marked difference in frequency among the various drugs and is also limited by misleading percentages created by low numbers of cases for some drugs.

DISCUSSION

In this study, the 2 most commonly occurring SGAs, quetiapine and olanzapine, made up over 80% of the SGA sample. Both drugs have significant histamine receptor blockade associated with central nervous system (CNS) depression.[8] Therefore, it is not surprising that higher rates of respiratory depression were observed in cases involving these drugs and that the odds of respiratory depression and coma would be greater overall for SGAs than for FGAs, given the prominence of these 2 drugs in the SGA sample. The higher odds of endotracheal intubation and mechanical ventilation for SGAs compared to FGAs are consistent with the higher rates of CNS depression observed with the SGAs. Similarly, the higher odds of having a major adverse outcome with SGAs are consistent with the higher rates of intubation and ventilation, since by definition the use of such interventions constitutes a major adverse outcome. While low-potency FGAs are also associated with CNS depression,[20] the low-potency FGAs in our sample, chlorpromazine, mesoridazine, and thioridazine, comprise slightly less than 50% of the overall FGA sample. Thus, the SGA sample still appears relatively weighted toward CNS-depressing agents compared to the FGAs.

Hypotension was a common side effect of both FGAs and SGAs, but the odds of hypotension being involved in a case were significantly higher for the SGAs. Antipsychotic-induced hypotension is usually associated with α_1 adrenergic blockade,[20] which among FGAs is more pronounced for the low-potency drugs. As noted above, these drugs made up about half of the FGA sample. Among the SGAs, quetiapine, olanzapine, and risperidone all have significant α_1 adrenergic blockade,[8] and all 3 drugs had hypotension as one of the most common symptoms reported. As these 3 drugs collectively make up 95% of our SGA sample, it is not surprising that the odds of hypotension were greater for the SGAs than for the FGAs. The increased odds of IV fluid use for SGA ingestions may reflect attempts to treat the observed hypotension, although there was no significant difference in vasopressor use between SGA and FGA cases.

The odds of dystonia and rigidity were both greater for FGAs than SGAs, likely a result of the FGAs' antagonism of postsynaptic dopamine receptors in the basal ganglia without the SGAs' mediating effect of serotonergic antagonism on the presynaptic dopaminergic cells.[6] The higher odds of possible or likely NMS cases observed

Table 4. Frequency of Adverse Outcomes, Symptoms, and Treatments by Specific Drug, N (%)[a]

Drug	No. of cases	Outcome: Minor Adverse Effect	Outcome: Moderate Adverse Effect	Outcome: Major Adverse Effect	Outcome: Death	Respiratory Depression	Coma	Hypotension
Second-generation antipsychotic								
Aripiprazole	17	7 (41.2)	10 (58.8)					1 (5.9)
Clozapine	37	16 (43.2)	17 (46.0)	4 (10.8)		2 (5.4)	5 (13.5)	3 (8.1)
Olanzapine	333	151 (45.4)	155 (46.6)	27 (8.1)		12 (3.6)	34 (10.2)	21 (6.3)
Quetiapine	939	407 (43.3)	420 (44.7)	109 (11.6)	3 (0.3)	49 (5.2)	96 (10.2)	165 (17.6)
Risperidone	220	121 (55.0)	96 (43.6)	3 (1.4)			1 (0.5)	29 (13.2)
Ziprasidone	22	14 (63.6)	8 (36.4)					2 (9.1)
Total no. of second-generation antipsychotics	1568	716	706	143	3	63	136	221
First-generation antipsychotic								
Chlorpromazine	117	70 (59.8)	40 (34.2)	7 (6.0)		4 (3.4)	8 (6.8)	10 (8.6)
Fluphenazine	25	12 (48.0)	13 (52.0)					
Haloperidol	99	36 (36.4)	60 (60.6)	3 (3.0)		2 (2.0)	2 (2.0)	8 (8.1)
Molindone	4	1 (25.0)	3 (75.0)					1 (25.0)
Mesoridazine	3	2 (66.7)		1 (33.3)				
Perphenazine	33	13 (39.4)	20 (60.6)					2 (6.1)
Pimozide	1		1 (100)					1 (100)
Thioridazine	82	40 (48.8)	33 (40.2)	9 (11.0)		1 (1.2)	5 (6.1)	10 (12.2)
Thiothixene	26	15 (57.7)	9 (34.6)	2 (7.7)			1 (3.9)	2 (7.7)
Trifluoperazine	15	8 (53.3)	6 (40.0)	1 (6.7)			1 (6.7)	
Zuclopenthixol	2		2 (100)					
Total no. of first-generation antipsychotics	407	197	187	23	0	7	17	34

[a]Percentages of symptoms and treatments do not sum to 100% since a given case could involve multiple symptoms and treatments and not all possible symptoms and treatments coded by California Poison Control System are included in this table.
Abbreviation: NMS = neuroleptic malignant syndrome.

with the FGAs may also be accounted for by this same mechanism of D_2 receptor antagonism without serotonergic mediation, although the pathophysiology of NMS is incompletely understood.[21,22]

Although our study did not detect significant differences in QRS widening or QT prolongation between SGAs and FGAs, this finding must be tempered by the fact that, for the large majority of the cases, no QRS or QT information was available for analysis. A substantial proportion of the FGA major adverse effect cases were related to cardiac conduction abnormalities and usually involved thioridazine, a drug well known for its quinidine-like effects on cardiac conductance.[23] In contrast, data on potential cardiac conduction disturbances by SGAs were not as well established until recently.[24,25] Because QRS and QT information was not routinely collected by poison center specialists for the cases, the cardiac conduction results could be subject to reporting bias: clinicians contacting the CPCS and poison center specialists collecting information may have paid more attention to potential cardiac problems by the FGAs than the SGAs.

No cases of serotonin syndrome were detected in our study using Hunter Serotonin Toxicity Criteria; however, several factors mitigate this finding. The Hunter Serotonin Toxicity Criteria rely heavily on specific neurological findings (e.g., spontaneous, ocular, or inducible clonus; hyperreflexia) to make the diagnosis. Clinicians contacting the CPCS may not have performed these diagnostic maneuvers to assess for serotonin syndrome. Similarly, because information about clonus or hyperreflexia is not routinely collected by poison center specialists, cases in which a tremor was reported may in fact have involved clonus or hyperreflexia without specifically being recorded.

While 2 of the 3 deaths observed in our sample were attributed to quetiapine, deaths from overdose of risperidone,[26] olanzapine,[27] and clozapine[28] have all been reported, as well as a pediatric case involving ziprasidone.[29] Both quetiapine-related deaths in our study were associated with respiratory depression and were complicated by aspiration pneumonia. Other researchers have suggested this is the typical clinical course for fatal SGA overdoses.[8,30] Deaths from FGAs have been well documented[23,31,32]; however, none were observed in our study.

There are several limitations to this study. The number of cases in our study involving a particular drug is likely to be a function of its relative prevalence in the United States and not just its potential for toxicity. Furthermore, our study only included cases in which CPCS was contacted. An unknown number of other cases may have been managed without coming to the attention of CPCS, leaving the frequency and severity of cases in this retrospective study subject to reporting bias. For example, antipsychotic-induced dystonia is an easily treatable condition, but, subjectively, dystonia can be very distressing for the patient and the treating physician. This distress could lead to a variable threshold for contacting CPCS for assistance. In contrast, clinicians might feel relatively

Symptom								Treatment			
Long QT	Wide QRS	Dystonia	Rigidity	Rhabdomyolysis	Fever	Possible or Likely NMS	Seizure	Intubation	Ventilation	Intravenous Fluids	Vasopressors
3 (17.7)		6 (35.3)								3 (17.7)	
		2 (5.4)	1 (2.7)	1 (2.7)		1 (2.7)	3 (8.1)	8 (21.6)	8 (21.6)	12 (32.4)	
8 (2.4)	2 (0.6)	6 (1.8)	2 (0.6)	2 (0.6)	7 (2.1)	1 (0.3)	6 (1.8)	51 (15.3)	35 (10.5)	101 (30.3)	3 (0.9)
48 (5.1)	16 (1.7)	5 (0.5)		3 (0.3)	4 (0.4)		20 (2.1)	149 (15.9)	87 (9.3)	324 (34.5)	19 (2.0)
12 (5.5)	3 (1.4)	19 (8.6)	4 (1.8)	2 (0.9)	2 (0.9)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.5)	53 (24.1)	3 (1.4)
2 (9.1)		1 (4.6)						2 (9.1)	1 (4.6)	7 (31.8)	
73	21	39	7	8	13	4	30	212	132	500	25
6 (5.1)	1 (0.9)	4 (3.4)			1 (0.9)		1 (0.9)	11 (9.4)	7 (6.0)	27 (23.1)	1 (0.9)
1 (4.0)	1 (4.0)	7 (28.0)				1 (4.0)		1 (4.0)		3 (12.0)	
3 (3.0)		39 (39.4)	4 (4.0)	3 (3.0)	4 (4.0)	4 (4.0)	1 (1.0)	4 (4.0)	1 (1.0)	19 (19.2)	1 (1.0)
	1 (25.0)									3 (75.0)	
			1 (33.3)							1 (33.3)	
2 (6.1)		7 (21.2)	1 (3.0)				1 (3.0)			4 (12.1)	
1 (100)										1 (100)	
14 (17.1)	5 (6.1)	2 (2.4)			1 (1.2)		1 (1.2)	7 (8.5)	5 (6.1)	16 (19.5)	3 (3.7)
		4 (15.4)								5 (19.2)	
1 (6.7)		4 (26.7)						1 (6.7)		2 (13.3)	
		2 (100)									
28	8	69	6	3	6	5	4	24	13	81	5

more comfortable managing antipsychotic-induced sedation without assistance from CPCS and thus not seek additional support from CPCS unless the sedation was severe enough to cause respiratory compromise. The CPCS data also lack sufficient QRS or QT information to draw firm conclusions about cardiac conduction abnormalities for SGAs versus FGAs, as mentioned earlier.

Another limitation is that the CPCS data do not include measurements of the concentration of the drug involved in the ingestions. The total number of milligrams of a drug ingested is recorded in the CPCS database in a small minority of cases. Even in those cases, the ingested amount was usually based on the patient's self-report and not independently verified through witnessed ingestion or pill counts. Time of arrival to health care facilities and decontamination procedures after arrival varied among cases as well; thus, initially equivalent ingestions could still result in different final levels of absorption. None of the cases had a serum concentration of an FGA or SGA recorded. For these reasons, it is possible that the average doses involved in the cases are not equivalent between the SGAs and FGAs.

A final limitation is that there are substantial differences in receptor affinity and side effect profiles among the individual SGAs and FGAs. With such variability among drugs, it may seem inappropriate to compare an entire class of diverse agents against another class of diverse agents. Despite this diversity of individual drugs, however, the overwhelming majority of antipsychotic drugs prescribed in the United States are SGAs,[1] and the goal of this study was to determine, from a safety standpoint, whether that preference for this class of drugs is warranted.

In the treatment of depression, the newer generation of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have been favored over the older tricyclic antidepressants (TCAs).[33] This preference is not due to superior efficacy for SSRIs over TCAs,[33,34] but rather due to other factors: a more benign side effect profile for SSRIs compared to TCAs[33,34] and markedly improved safety of SSRIs in acute overdose compared to TCAs.[35,36] As the risk for suicide among schizophrenic patients is also high, safety in acute overdose appears to be a reasonable factor to consider when selecting an antipsychotic medication. Unlike the SSRIs versus the TCAs, however, we do not find a clear safety advantage for SGAs over FGAs following acute ingestion of a toxic dose.

In conclusion, our review of 1975 cases of acute SGA or FGA toxic ingestion revealed that the odds of a major adverse outcome or death were significantly higher with SGAs than with FGAs, suggesting that the SGAs are not safer in acute overdose. The odds of respiratory depression, coma, and hypotension were higher with the SGAs, whereas the odds of dystonia and rigidity were higher with the FGAs. Adverse reactions produced by SGAs, such as CNS depression, may seem more mundane than the dystonia or rigidity that FGAs can produce. However, respiratory depression and coma can be life threatening,

and the drugs that cause them should be prescribed with caution.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon).

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