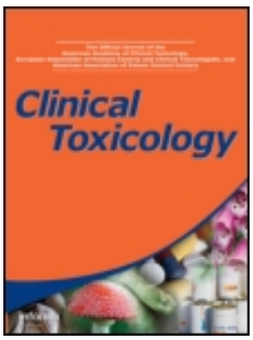

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PRACTICE GUIDELINE

Atypical antipsychotic medication poisoning: An evidence-based consensus guideline for out-of-hospital management*

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The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and out-of-hospital management of patients with suspected acute ingestions of atypical antipsychotic medications by 1) describing the process by which an ingestion of an atypical antipsychotic medication might be evaluated, 2) identifying the key decision elements in managing cases of atypical antipsychotic medication ingestion, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This guideline applies to ingestion of atypical antipsychotic medications alone. Co-ingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances. This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions might be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment. The grade of recommendation is in parentheses. 1) Patients with stated or suspected self-harm or the recipient of a potentially malicious administration of an atypical antipsychotic medication should be referred to an emergency department immediately. This activity should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (Grade D). 2) Patients without evidence of self-harm should have further evaluation, including determination of the precise dose ingested, presence of signs or symptoms of toxicity, history of other medical conditions, and the presence of co-ingestants (Grade C). 3) Asymptomatic patients without evidence of attempted self-harm are unlikely to develop symptoms if the interval between the ingestion and the call is greater than 6 hours. These patients do not need referral and should receive follow-up based on local poison center protocols (Grade C). 4) All patients less than 12 years of age who are naïve to atypical antipsychotic medications and are experiencing no more than mild drowsiness (lightly sedated and can be aroused with speaking voice or light touch) can be observed at home unless they have ingested more than four times the initial adult dose for the implicated antipsychotic medication or a dose that is equal to or more than the lowest reported acute dose that resulted in at least moderate toxicity, whichever dose is smaller (i.e., aripiprazole 15 mg, clozapine 50 mg, olanzapine 10 mg, quetiapine 100 mg, risperidone 1 mg, ziprasidone 80 mg) (Grade D). 5) All patients 12 years of age or older who are naïve to atypical antipsychotic medications and are experiencing no more than mild drowsiness can be observed at home unless they have ingested more than five times the initial adult dose for the implicated antipsychotic medication (i.e., aripiprazole 50 mg, clozapine 62.5 mg, olanzapine 25 mg, quetiapine 125 mg, risperidone 5 mg, ziprasidone 100 mg) (Grade D). 6) Patients who use atypical antipsychotic medications on a chronic basis can be observed at home unless they have acutely ingested more than 5 times their current single dose (not daily dose) of the implicated antipsychotic medication (Grade C). 7) Patients who have ingested less than a threshold dose (see Recommendations 4–6) and are exhibiting no more than mild drowsiness can be observed at home with instructions to call the poison center if symptoms develop or worsen. If mild drowsiness is present at the time of the initial call, the poison center should make follow-up calls until at least 6 hours after ingestion. Consideration should be given to the time of day that home observation will take place. Observation during normal sleep hours might not be reliable. Depending on local poison center policy, patients could be referred to an emergency department if the observation would take place during normal sleeping hours of the patient or caretaker (Grade D). 8) Any patient already experiencing any signs or symptoms, other than mild drowsiness, thought to be related to atypical antipsychotic medication toxicity should be transported to an emergency department. Transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department (Grade D).

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9) Do not induce emesis (Grade D). 10) There are no specific data to suggest benefit from out-of-hospital administration of activated charcoal in patients exposed to atypical antipsychotic medications. Poison centers should follow local protocols and experience with the out-of-hospital use of activated charcoal in this context. Do not delay transportation in order to administer charcoal (Grade D). 11) For patients who merit evaluation in an emergency department, transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department. Continuous cardiac monitoring should be implemented given reports of conduction disturbances associated with this class of medications. Provide usual supportive care en route to the hospital, including airway management and intravenous fluids for hypotension (Grade D). 12) Depending on the specific circumstances, follow-up calls should be made to determine outcome at appropriate intervals based on the clinical judgment of the poison center staff (Grade D).

Keywords Antipsychotics; Atypical/poisoning; Poison control centers/standards; Practice guidelines

Introduction

Scope of the problem and importance of the guideline

From 2001 through 2005, poison centers (PCs) in the US reported 156,431 ingestions of atypical antipsychotic medications to the Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers. When 2001 and 2005 were compared, there was a 97% increase in the number of reported ingestions of this class of medications. Of these ingestions, 46,950 (30%) were unintentional and 12,360 (7.9%) involved children less than 6 years of age. The majority of cases reported involved adults and were intentional in nature. Most patients (120,955 or 77.3%) were referred to or had already presented to healthcare facilities. There were 8894 (5.7%) major effect outcomes and 403 (0.3%) deaths reported from 2001 through 2005. The growing number of reported ingestions of these agents and their potential toxicity led to a systematic review of available evidence and development of consensus-based triage guidelines.

The atypical antipsychotic medications currently available in the US are aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone (see Table 1 for products and dosages).

Pharmacology and pharmacokinetics

Atypical antipsychotics have been shown to have beneficial impacts on both the positive and negative symptoms of schizophrenia and are also used to treat psychotic, bipolar, and autistic disorders. There are also reports of off-label use for conditions such attention deficit-hyperactivity disorder (1).

Atypical antipsychotic medications are tricyclic dibenzothiazepines that have less potential to cause extrapyramidal effects, tardive dyskinesia, and elevation of serum prolactin concentrations than the phenothiazine and butyrophenone antipsychotics. These medications first became available in the US with the approval of clozapine in 1990. They variably antagonize both serotonin ($5\text{-}HT_{2A}$) and dopamine (D_2, D_4, D_6, and D_7) receptors. When compared to phenothiazines and butyrophenones, atypical antipsychotic medications have a greater binding affinity for the $5\text{-}HT_2$ receptors than for D_2 receptors (2). However, they also have the ability to bind to $5\text{-}HT_1$, multiple dopamine, $alpha_1$ adrenergic, and $histamine_1$ receptors. Aripiprazole is thought to differ from other atypical antipsychotic medications as it has partial agonist activity at the D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors (3). The decreased incidence of extrapyramidal effects of the atypical antipsychotic medications, when compared to typical antipsychotics, is attributed to the differences in their receptor binding affinities.

The clinical manifestations of atypical antipsychotic toxicity generally include varying degrees of central nervous system depression, anticholinergic effects, pupillary changes, seizures, hypotension, and cardiac conduction abnormalities. Clozapine has been shown to cause agranulocytosis in 1–2% of patients after 1 year of therapy (4).

The absorption kinetics profiles of the atypical antipsychotic medications are varied. Aripiprazole peak plasma concentrations are reached within 3–5 hours. High fat meals might decrease the rate of absorption but not overall bioavailability (3). Clozapine is rapidly and completely absorbed with the peak serum concentration occurring 1½–2½ hours after a single dose (5). Following oral administration, olanzapine is well absorbed and peak plasma concentration is reached at approximately 6 hours (6). Quetiapine is rapidly absorbed after oral administration. Peak plasma concentrations are expected within 1½ hours of dose administration (7). Risperidone is extensively and rapidly absorbed with peak plasma concentrations at 1 hour after a dose. Oral tablets have an absolute bioavailability of approximately 70% while the solution has a 94% absolute bioavailability (8). Following oral administration of ziprasidone to fed subjects, peak plasma concentrations occurred at 6–8 hours (9).

Aripiprazole, olanzapine, quetiapine, risperidone are all classified as FDA Pregnancy Risk Category C. Clozapine is classified as Category B.

Definition of terms used in this guideline

Toxicity from atypical antipsychotic medications might occur as a result of a single acute ingestion, which could be unintentional or intentional, or with repeated or therapeutic use. An acute exposure might involve unintentional ingestion of a second therapeutic dose by a patient already on the drug, unintentional ingestion of someone else's therapeutic dose by a patient naïve to atypical antipsychotic medications, unintentional ingestion by a child, or ingestion with suicidal intent.

Table 1. Atypical antipsychotic medications available in the US, 2006 (3,4,6–9)

Generic name	Brand name(s)	Available formulations	Adult daily dosage range	Initial pediatric doses* (Ref.)
Aripiprazole	Abilify	2, 5, 10, 15, 20, 30 mg tablets	10–15 mg	Not available
		1 mg/mL oral solution	Concomitant CYP3A4 inducer use: 20–30 mg	
		9.75 mg/1.3 mL single-dose vial for injection	9.75 mg	
	Abilify Discmelt	10, 15 mg orally disintegrating tablets	10–15 mg	
Clozapine	Clozaril	25, 100 mg tablets	12.5–900 mg	6.25–25 mg (125, 136)
Olanzapine	Zyprexa	2.5, 5, 7.5, 10, 15, 20 mg tablets	5–15 mg In debilitated patients, those predisposed to hypotension, and slow metabolizers: 5 mg/d starting dosage	1.25 mg (212, 124, 126, 131)
		10 mg powder for injection/unit-dose vial	2.5–10 mg	
	Zyprexa Zydis	5, 10, 15, 20 mg orally disintegrating tablets	5–15 mg	
Quetiapine	Seroquel	25, 100, 200, 300, 400 mg tablets	25 mg twice daily up to 800 mg/d Patients with hepatic dysfunction: start at 25 mg/d	Not available
Risperidone	Risperdal	0.25, 0.5, 1, 2, 3, 4 mg tablets	1 mg twice daily up to 8 mg/d	0.125 mg (122–124, 127–130)
	Risperdal M-TAB	0.5, 1, 2, 3, 4 mg orally disintegrating tablets	Patients who are elderly, debilitated, predisposed to hypotension, or who have renal/hepatic impairment: 0.5–3 mg	
	Risperdal Oral Solution	1 mg/mL oral solution		
	Risperdal Consta	25, 37.5, 50 mg powder for injection/unit-dose vials	25–50 mg every 2 weeks	
Ziprasidone	Geodon	20, 40, 60, 80 mg capsules	20 mg twice daily up to 160 mg/d	Not available
		20 mg powder for injection/unit-dose vial	10 mg every 2 hr or 20 mg every 4 hr up to 40 mg/d	

*The cited studies enrolled patients as young as 3 years of age, with most starting at 4–5 years of age.

This guideline focuses on the ingestion of more than a single therapeutic dose. It is known that even therapeutic doses of atypical antipsychotic medications can sometimes cause adverse effects in both adults and children—some idiosyncratic and some dose-dependent.

For the purpose of this guideline, age groups were initially defined as 1) children less than 12 years of age and 2) older children and adults. Acute exposures are defined as those occurring over a period of no more than 8 hours. The term "out-of-hospital" is defined as the period before a patient reaches a healthcare facility.

Exclusions

This guideline does not provide guidance on exposures to typical antipsychotics, such as phenothiazines and butyrophenones, which have different pharmacological effects and toxicity profiles. Furthermore, this guideline does not address management of patients who experience chronic toxicity or adverse effects from chronic atypical antipsychotic medication use such as their endocrine effects and clozapine-associated agranulocytosis.

Intended users of this guideline

The intended users of this guideline are personnel in US poison centers. This guideline has been developed for the conditions prevalent in the US. While the toxicity of common atypical antipsychotic medications is not expected to vary in a clinically significant manner in other nations, available formulations and active ingredients might differ for some atypical antipsychotic medications. In addition, out-of-hospital

conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.

Objective of this guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and out-of-hospital management of patients with suspected acute ingestions of atypical antipsychotic medications by 1) describing the process by which an ingestion of an atypical antipsychotic medication might be evaluated, 2) identifying the key decision elements in managing cases of atypical antipsychotic medication ingestion, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This guideline applies to ingestion of atypical antipsychotic medications alone. Exposure to additional substances could require different referral and management recommendations depending on the combined toxicities of the substances.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment.

Methodology

The methods used for the preparation of this guideline were developed after reviewing the key elements of practice guidelines (10,11). An expert consensus panel was established to develop the guideline (Appendix 1). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional track record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US poison center experience, and be an opinion leader with broad esteem. Two specialists in poison information were included as full panel members to provide the viewpoint of potential end-users of the guideline.

Literature search

Literature searches for relevant articles were performed by a single investigator. The National Library of Medicine's PubMed database was searched (through April 2005) using clozapine or risperidone as MeSH terms with the subheadings "poisoning" or "toxicity" limited to humans. A second PubMed search used aripiprazole, clozapine, olanzapine, quetiapine, risperidone or ziprasidone as textwords (title, abstract, MeSH term, CAS registry) in conjunction with the textwords poison*, intoxicat*, overdos*, or toxic*, limited to humans. The CAS registry numbers for these compounds were also used as search terms. This process was repeated in International Pharmaceutical Abstracts (1970–2004, excluding abstracts of meeting presentations), Science Citation Index (1977–2004), Database of Abstracts of Reviews of Effects (accessed December 2004), Cochrane Database of Systematic Reviews (accessed December 2004), and Cochrane Central Register of Controlled Trials (accessed December 2004), and Reactions (1980–2004). A third PubMed search used the list of atypical antipsychotics and selected all articles with these drugs and the age categories 1–23 months and 2–5 years. The relevant poisoning managements in Poisindex and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology abstracts published in the Journal of Toxicology Clinical Toxicology (1995–2004) were reviewed for original human data.

The chapter bibliographies in five toxicology textbooks were reviewed for citations of additional articles with original human data. The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers, was searched for deaths resulting from atypical antipsychotic medication poisoning or any deaths from atypical antipsychotic medication poisoning in children. These cases were abstracted for use by the panel. The package inserts from marketed atypical antipsychotic medications were reviewed for any mention of overdose experience.

Criteria used to identify applicable articles

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, searching specifically for those that dealt with estimations of doses, with or without subsequent signs or symptoms of toxicity, and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles were excluded if they did not meet either of the preceding criteria, did not add new data (e.g., reviews, editorials), or if they exclusively described inpatient-only procedures (e.g., dialysis).

Data extraction

All articles that were retrieved from the search were reviewed by a trained physician abstractor. Each article was examined for original human data regarding the toxic effects of atypical antipsychotic medications or original human data directly relevant to the out-of-hospital management of patients with

atypical antipsychotic medication toxicity or overdose. Relevant data (e.g., dose, resultant effects, time of onset of effects, therapeutic interventions or decontamination measures given, effectiveness or results of any interventions, and overall patient outcome) were compiled into a table and a brief summary description of each article was written. The evidence table includes levels of severity as defined by the expert consensus panel. These severity levels are used throughout this guideline and are defined as follows: mild—local effects only or mild systemic effects (e.g., sedated but arousable, agitated), moderate—systemic effects (e.g., more severe sedation or agitation, tachycardia, hypertension, hyperthermia, ECG abnormalities), and severe—life-threatening systemic effects (e.g., severe hyperthermia or rigidity, coma or sedation requiring intubation, seizures, respiratory depression, hypotension, dysrhythmias).

This full evidence table is available at (http://www.aapcc.org/DiscGuidelines/atypical%20antipsychotics%20evidence%20table%202005-8-29.pdf). The completed table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Efforts were made to locate significant foreign language articles and have their crucial information extracted, translated, and tabulated. Copies of all of the articles were made available for reading by the panel members on a secure AAPCC website.

Criteria used to assign levels of evidence

The articles were assigned level-of-evidence scores by the abstractor based on the Grades of Recommendation table developed by the Centre for Evidence-Based Medicine at Oxford University (Appendix 2). Single case reports and case series were classified as level 4.

Guideline writing and review

A guideline draft was prepared by the lead author (listed first). The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, copied into a table of comments, and submitted to the lead author for response. The lead author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the lead author, the draft was prepared for the external review process. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the AAPCC web site or privately through email communication to AAPCC staff. All submitted comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the lead author. The lead author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel.

Evaluation of evidence

Current poison center practice

The expert consensus panel solicited referral and management guidelines for atypical antipsychotic medications from US poison centers in 2004 and received one document from a poison center. Five other centers indicated that they did not have any written guidelines for atypical antipsychotic poisoning. The remaining centers did not respond to the request. Review of the submitted guideline did not reveal recommendations for triage doses or out-of-hospital gastrointestinal decontamination.

Review of textbooks

The review of the atypical antipsychotic poisoning chapters in five toxicology textbooks revealed little variation in their recommendations (12–16). In providing their treatment recommendations, none of the authors differentiated between treatments for atypical vs. typical antipsychotic exposures, and none provided guidance on out-of-hospital triage doses. Most of the authors advised that ipecac syrup was contraindicated as a gastrointestinal decontamination method in patients exposed to atypical antipsychotics. A single dose of activated charcoal was recommended in all of the chapters and one author (13) recommended use of a cathartic along with activated charcoal. Administration of crystalloids (e.g., saline solution) followed by α-adrenergic agonists (e.g., dopamine) if necessary, was routinely recommended for the treatment of antipsychotic-induced hypotension.

Review of Poisindex

This toxicology information resource did not provide any specific recommendations regarding doses at which emergency department referral is appropriate. Poisindex advised against the use of ipecac syrup to induce emesis. Information was provided on the use of activated charcoal and sign/symptom-specific supportive care (17).

Review of TESS mortality data

The American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database was analyzed

for deaths from atypical antipsychotic poisoning over a 20-year period (1985–2004). Only deaths involving an atypical antipsychotic alone were investigated. Clozapine [7], olanzapine [9], quetiapine [14], and risperidone [5] were each implicated in the fatality cases. Six of these deaths were subsequent to unintentional ingestions, 27 were intentional in nature, and the exposure reason was unknown in two cases. One was due to an unintentional poisoning in a child, two resulted from adverse drug reactions, and one was due to a therapeutic error. The pediatric poisoning death involved a 2-year-old girl who reportedly chewed one clozapine 100-mg tablet (10 mg/kg) and became ataxic 1 hour after the ingestion. En route to an emergency department she vomited, and she was obtunded upon arrival. She subsequently experienced another episode of vomiting and developed aspiration pneumonia, sepsis, and anemia. She died on the 16th hospital day.

Review of the medical literature

For the purposes of guideline preparation, a written summary of the evidence from all the reviewed articles on the selected atypical antipsychotics appears below. There were few articles that specifically addressed out-of-hospital management for any of these agents. However, there were a number of articles with some limited out-of-hospital information. The expert consensus panel believed that much of the in-hospital data could be applied and extrapolated to help develop the out-of-hospital guidelines. Therefore, both in- and out-of-hospital data are included in the following summary of the evidence.

There were numerous limitations associated with the available evidence. There was a paucity of high quality studies and there were no prospective trials specifically investigating a toxic threshold dose for individual atypical antipsychotic agents. A small number of retrospective articles contained some dose-effect information on specific agents. The accuracy of dose estimates in most articles was unclear. Retrospective data from case reports or case series were often confounded by concomitant exposures to other substances, medical co-morbidities, or differences in decontamination and treatment measures. Each of these could have altered the clinical presentation or outcome. The evidence was also influenced by inter-individual differences in age, weight, underlying health condition, and genetic factors that might also have affected the clinical response. In some of the larger reviews, the ingested amounts and/or the resultant effects were reported as a range of values or percentages of patients. Therefore, individual doses resulting in specific effects could not be determined. In the prospective trials reviewed, the medications were administered at therapeutic doses that were lower than those likely to occur in the setting of an overdose or poisoning.

Despite these limitations, the available dose-response information extracted from the evidence is summarized below. It is divided into two categories—acute ingestions in children less than 12 years of age and acute ingestions in patients 12 years of age and older. These data were further divided into subcategories based on the specific atypical antipsychotic medication involved. All of the reviewed articles, whether cited here or not, are abstracted in detail in evidence table.

When the mg/kg dose or a child's weight was not stated in an article for patients less than 12 years of age, the mg/kg dose was estimated by the use of pediatric growth charts (18). The 95th percentile weight was used for a particular age and sex. When the sex of the child was not stated, the weight for boys was used. This approach errs on the side of estimating a lower mg/kg dose. Estimated mg/kg doses are italicized throughout the guideline whenever they are presented.

Acute ingestions in children less than 12 years of age (see Table 2)

Aripiprazole

There were six level 4 or 6 articles with information on acute aripiprazole ingestions in patients less than 12 years of age. From these, the lowest dose associated with any toxicity was 15 mg (0.6 mg/kg) in a 9-year-old girl who was hospitalized for prolonged somnolence that began 3½ hours after ingestion (level 4). She was also being treated with valproic acid (serum concentration below 10 μg/mL) and amphetamine (19). A case series (level 4) described aripiprazole toxicity following eight overdoses. Patient ages ranged from 3 to 43 years with a mean of 24 years. Four of the cases were due to unintentional ingestion. Based on data from six patients, the authors reported a mean dose of 82 mg; no range was provided. In the unintentional ingestion group, three of the four patients were observed at home without any untoward effects. The fourth patient in this group was observed in an emergency department and had no signs of toxicity. In the intentional ingestion group, all four patients were observed in an ED and two were admitted due to extensive sedation (20). A 3-year-old boy, who ingested an estimated 11.9 mg (*0.8 mg/kg*), developed extreme lethargy, flat affect, tremor, ataxia, and a parkinsonian gait. However, this dose was estimated based on back-extrapolation from the serum drug concentration (21). A 2-year-old girl who ingested 40 mg (*2.4 mg/kg*) developed vomiting and lethargy (level 6) (22). A case report (level 4) described a 2½-year-old girl who ingested 195 mg (17.1 mg/kg) and developed vomiting, tremulousness, ataxia, lethargy, and coma (23). An epidemiologic study of aripiprazole ingestions reported to Texas poison control centers (level 4) found that aripiprazole-alone ingestions most often involved children less than 6 years of age. Clinical effects most often reported included drowsiness and lethargy (24). The package insert for Abilify mentions 10 overdoses in children (aged 12 years and younger) with doses up to 195 mg with no fatalities (3).

Table 2. Acute toxicity in patients less than 12 years of age

Drug	Dose	Age	Mitigating factors	Effect*	Symptom onset†	Confirm. Conc.?‡	Ref. (LOE)
Aripiprazole	Description of 8 aripiprazole ingestions (avg. age 24 years, range 3–43) reported to a PC. Avg. dose was 82 mg. Three of 4 accidental ingestions were watched at home and all of the intentional ingestions were referred to EDs. Two intentional ingestions were admitted for excessive somnolence. All had "favorable outcomes."						20 (4)
	15 mg [0.6 mg/kg]	9 yr	On amphetamine and valproic acid	Mod	3½ hr	NR	19 (4)
	20 mg [*0.7 mg/kg*]	6 yr	NR	Mod	>24 hours	NR	137 (4)
	~11.9 mg [*0.8 mg/kg*] (based on calculation from serum drug conc.)	3 yr	NR	Mod	≤48 hr	B	21 (4)
	40 mg [*2.4 mg/kg*]	2 yr	NR	Mild	NR	NR	22 (6)
	195 mg [17.1 mg/kg]	3½ yr	NR	Mod/Severe	<1 hr	B	23 (4)
Clozapine	Description of 150 clozapine ingestions (143 adult and 7 pediatric) reported to the manufacturer or in the literature (some of these cases could therefore appear elsewhere in this summary); doses 50–25,000 mg; all of the children developed mild to severe clinical effects; lowest dose associated with severe toxicity in a child was <500 mg.						25 (4)
	100 mg [*2.1 mg/kg*]	10 yr	NR	Mod	<24 hr	U	27 (4)
	~50 mg (one-half of a 100-mg tablet) [2.6 mg/kg]	21 mo	NR	Severe	NR	NR	Mady (4)
	100 mg [4.8 mg/kg]	4 yr	NR	Mod	~1 hr	B	28 (4)
	100–200 mg [8.7–17.4 mg/kg]	31 mo	NR	Severe	<3 hr	B	28 (4)
	200 mg [10 mg/kg]	5 yr	NR	Severe	Soon after	B	29 (6)
	Description of 8 clozapine-only ingestions (ages 2–42 yr); doses 1100–5500 mg; >66% developed at least some clinical effects.						26 (4)
Olanzapine	Abstract of 12 olanzapine ingestions (11 adults and 1 child); doses 25–135 mg (7 cases had co-ingestants) in the adults; some developed mild–moderate effects.						62 (6)
	10 mg [0.6 mg/kg]	6 yr	Asthma	Mod	<15 hr	NR	30 (6)
	Up to 15 mg [*0.9 mg/kg*]	2½ yr	NR	Mod	≤10 hr	B	32 (6)
	30–40 mg [2.7–3.6 mg/kg]	18 mo	NR	Severe	<2 hr	B	33 (4)
	100 mg [3.4 mg/kg]	9 yr	Also ingested acetaminophen	Severe	≤2 hr	NR	31 (4)
Quetiapine	1300 mg [22.2 mg/kg]	11 yr	NR	Mod	<1 hr	NR	34 (4)
Risperidone	Abstract describing 31 risperidone ingestions (adult and pediatric); doses 1–150 mg (15 had co-ingestants); some developed clinical effects ranging from mild to moderate.						38 (6)
	1 mg [*0.03 mg/kg*]	7 yr	NR	Mod	NR	NR	36 (6)
	1 mg [*0.07 mg/kg*]	16 mo	NR	None	NR	NR	35 (4)
	4 mg [*0.18 mg/kg*]	5 yr	Clonazepam	None	NR	NR	35 (4)
	4 mg [0.3 mg/kg]	3½ yr	ADHD, on clonidine and methylphenidate chronically; missed a methylphenidate dose	Severe	NR	NR	37 (4)
Ziprasidone	Description of 30 ziprasidone ingestions (avg. age 23 years, range 1–41) reported to a PC. Avg. dose was 206 mg. Seven of 8 accidental ingestions were watched at home and all of the intentional ingestions were referred to EDs. One patient ingested an unknown dose and presented comatose, required intubation, and recovered after 8 hours.. All others had "good outcomes."						41 (6)
	Abstract describing 7 ziprasadone-only ingestions: a 22-m.o. ingested 40 mg [*2.5 mg/kg*] and a 2-y.o. ingested 80 mg [5.2 mg/kg]; only the 2 y.o. developed effects. The other children were more 10–16 yrs of age.						39 (6)
	400 mg	17 mo	NR	Mod	<1 hr	NR	40 (4)

**Mild* = local effects only or mild systemic effects (e.g., sedated but arousable, agitated); *mod* = systemic effects (e.g., more severe sedation or agitation, tachycardia, hypertension, hyperthermia, ECG abnormalities); *severe* = life-threatening systemic effects (e.g., severe hyperthermia or rigidity, coma or sedation requiring intubation, seizures, respiratory depression, hypotension, dysrhythmias).

†maximal time of onset; (i.e., symptoms were present on admission, but might have begun earlier).

‡*B* = blood.

NR = not reported or none reported.

Clozapine

There were no level 1–3 articles with dose-toxicity information for clozapine. However, there were two level 4 reports that included patients less than 12 years of age with acute clozapine exposures from which some dose-toxicity information could be extracted. Unfortunately, these articles reported the doses as ranges, making it impossible to determine which patients had effects. Since the articles did not specify patient ages or included patients older than 12 years of age, it was impossible to determine which doses referred to patients of what age. The first paper was a description of 150 clozapine ingestions (143 adult and seven children) reported to the manufacturer or in the literature. The doses ingested ranged from 50 to 25,000 mg. The lowest dose resulting in any toxicity was not specified, but the mean dose in the seven children aged 1 to 5 years was 157 mg. All of the children developed clinical effects. These included sedation [7], tachycardia [1], hypotension [1], and hypersalivation [2] (25). The second report included eight clozapine-only ingestions in patients between 2 and 42 years of age reported to one PC over a 9-month period. Reported doses were between 1100 and 5500 mg, and most of the patients developed at least some clinical effects. These included confusion, aggression, agitation, CNS depression, respiratory depression, tachycardia, hypertension, vomiting, mydriasis, dysarthria, dystonia, and increased muscle tone/hyperreflexia (26). There were also five cases reported in three level 4 or 6 articles (27–29). In one case (level 4), a 21-month-old boy ingested one-half of a 100 mg clozapine tablet (2.6 mg/kg). He later developed pallor, sleepiness, and loss of coordination of his limbs and trunk. Upon presentation to an ED, he was pale, listless, and had peri-oral cyanosis (28). A 10-year-old girl ingested one 100-mg clozapine tablet (*2.1 mg/kg*). The next morning, she was difficult to arouse. She presented at an emergency department drowsy, confused, disoriented, and unable to walk, with alternating episodes of agitation and stupor, slurred speech, verbal and physical aggression, and hallucinations. Her CNS depression worsened during her second hospital day, and she requiring intubation. Full resolution of her symptoms occurred at approximately 55 hours after ingestion (27).

Olanzapine

There were no level 1–3 studies with dose-toxicity information on patients less than 12 years of age with acute olanzapine exposures. There were, however, six level 4 or 6 case reports. Among these, the lowest dose of olanzapine associated with toxicity (level 6) was 10 mg (0.6 mg/kg) in a 6-year-old girl who developed slurred speech, staggering gait, and lethargy during the first 15 hours after ingestion (30). The lowest dose associated with severe toxicity (level 4) was 100 mg (3.4 mg/kg) in a 9-year-old boy who had also ingested acetaminophen and, within 2 hours of ingestion, was reported to be combative, unable to follow commands, tachycardic, hypotensive, and experiencing decreased GI motility (31). A 2½-year-old boy was taken to an ED 9½ hours after a suspected ingestion of up to 15 mg of olanzapine (*0.9 mg/kg*) because of "abnormal behavior." Within 1 hour of presentation, he was sleepy and difficult to arouse. When awakened, he refused to interact and was slow to respond. The abstract (level 6) described him as hostile, agitated, glassy-eyed, violent, apparently in pain, and refusing to eat. An ECG showed tachycardia. At approximately 14 hours after presentation, his behavior was normal (32). In another case report (level 4), an 18-month-old boy reportedly ingested 30–40 mg of olanzapine (2.7–3.6 mg/kg). Ipecac syrup was administered in the prehospital setting. Upon presentation to an emergency department 2 hours after ingestion, he was somnolent and combative with respiratory depression, tachycardia, and decreased bowel sounds (33).

Quetiapine

In the only article (level 4) that contained information on a dose-toxicity relationship for quetiapine in patients less than 12 years of age, an 11-year-old girl ingested 1300 mg quetiapine (22 mg/kg). She was found stumbling and acting inappropriately and was brought to an emergency department 1 hour after ingestion. She was lethargic, mumbling, miotic, and laboratory test results showed hypokalemia. Three hours after ingestion, she became combative and agitated. She was treated with lorazepam, which this controlled her agitation, and she recovered over the next 24 hours (34).

Risperidone

A level 4 case series reported a 16-month-old boy who ingested 1 mg risperidone who was given activated charcoal and remained asymptomatic. A 5-year-old boy in the same series ingested 4 mg risperidone, along with clonazepam, and remained asymptomatic after receiving activated charcoal (35). The ingestion of 1 mg by a 7-year-old boy (level 6) resulted in confusion, lethargy, hypertonicity, drooling, a stiff tongue, orthostatic hypotension, and a sinus dysrhythmia with QTc prolongation (36). A case report (level 4) described a 3½-year-old boy who ingested 4 mg (0.3 mg/kg) risperidone and became unresponsive. He recovered over 2–3 days (37). There were no other level 1–4 articles with dose-toxicity information for risperidone. However, there was a level 6 abstract that included patients less than 12 years of age with acute risperidone ingestions and from which some dose-toxicity information could be obtained. The abstract was a review of 31 risperidone ingestions (adults and children) reported to one PC over a 15-month period. Doses ranging from 1 to 150 mg were reported (15 cases had co-ingestants) with some of the patients developing clinical effects ranging from mild to moderate in severity. Five patients in the group without co-ingestants were asymptomatic. Lethargy [8], tachycardia [2], and vomiting [1] were reported in the other 11 patients (38).

Ziprasidone

There were no level 1–3 articles with dose-toxicity information for ziprasidone. There was a single level 6 abstract of a

case series that included patients less than 12 years of age with acute ziprasidone exposure and from which some dose-toxicity information could be extracted. The abstract briefly mentioned seven pediatric ziprasidone ingestions (including one 2-year-old and a 22-month-old) reported to one PC over a 1-year period. The 22-month-old child had ingested 40 mg (*2.5 mg/kg*) and remained asymptomatic. The other child ingested 80 mg (*5.2 mg/kg*) and became somnolent (39). A case report (level 4) described a 17-month-old girl who developed drowsiness, miosis, tachycardia, and QTc prolongation following a reported exposure to ziprasidone 400 mg (*30 mg/kg*) (40). A case series (level 4) briefly described 30 ziprasidone ingestions reported to a PC. The mean dose ingested was 206 mg; no range was provided. Patients ranged in age from 1 to 43 years (mean 23 years). Of the eight accidental ingestions, seven were observed at home and the eighth was seen at an emergency department and discharged "without incident." Almost all (19/22) of the intentional ingestion patients were evaluated at emergency departments with one presenting comatose and requiring intubation but recovered after 8 hours. The age of this patient was not provided and the dose ingested was stated to be unknown (41).

Acute ingestions in patients 12 years of age and older (see Table 3)

Aripiprazole

A case series (level 4) described aripiprazole toxicity following eight overdoses. Patient ages ranged from 3 to 43 years with a mean of 24 years. Four of the cases were due to unintentional ingestion. Based on data from six patients, the authors reported a mean dose of 82 mg; no range was provided. In the unintentional ingestion group, three of the four patients were observed at home without any untoward effects. The fourth patient in this group was observed in an emergency department and had no signs of toxicity. In the intentional ingestion group, all four patients were observed in an ED and two were admitted due to extensive sedation (20). A case report (level 4) provided detailed information on a dose of aripiprazole associated with toxicity. In this case, a 27-year-old woman developed tachycardia and sedation after ingesting aripiprazole 330 mg along with quetiapine 25 mg (42).

The package insert for Abilify briefly describes an ingestion of 1080 mg apipiprazole with full recovery (3).

Clozapine

The package insert for Clozaril indicates that fatal overdoses have been reported for clozapine "…generally at doses above 2500 mg." It also indicates that patients have recovered from overdoses larger than 4 g.

There were no level 1–3 articles with dose-toxicity information for clozapine. However, there were three level 4 retrospective cases series that included patients 12 years of age and older with acute clozapine ingestions from which some dose-toxicity information could be extracted (25,26,43). These articles reported the doses as ranges, making it impossible to determine which patients had effects. Two of the articles (25,26) included patients less than 12 years of age, making it difficult to ascertain which doses referred to patients of what age. One was a description of 150 clozapine ingestions (143 adult and seven children) reported to the manufacturer or in the literature. Doses ranged from 50 to 25,000 mg. Clinical effects observed in the adult patients included sedation [103], agitation [25], seizures [12], tachycardia [44], hypotension [11], hypertension [2], ECG changes (e.g., AV block, extrasystoles, repolarization abnormalities, prolonged ST, "fibrillation") [15], cardiac failure [4], hypersalivation [11], renal effects [5], GI effects [7], and aspiration [14]. The lowest dose resulting in any toxicity was not specified. However, the lowest dose associated with severe toxicity was reported as being less than 500 mg (25). Another was a review of seven clozapine ingestions by patients aged 22–48 years reported to one toxicology service over a period of approximately 2 years. Doses ranged from 100 to 16,000 mg, and clinical effects observed included tachycardia [4], dysarthria [4], decreased Glasgow Coma Scale score [3], tachypnea [2], disconjugate gaze [1], weakness [1], sialorrhea [2], and decreased bowel sounds [1]. The lowest dose associated with mild effects was 100 mg and the lowest dose associated with severe toxicity was 1000 mg (43). There were also numerous level 4 and 6 articles with individual case information on acute clozapine ingestions in patients 12 years of age and older—18 cases reported in 17 articles (44–60). From these cases, the lowest dose of clozapine associated with any toxicity was 100 mg. This dose led to significant CNS depression in three patients (46,48) and hypotension and tachycardia in one (46).

Olanzapine

There were no level 1–3 articles with dose-toxicity information. However, there were three level 4 or 6 retrospective reviews that included patients 12 years of age or older with acute olanzapine ingestions from which some dose-toxicity information could be extracted (26,61,62). Most of these reviews reported the doses as ranges making it impossible to associate doses and effects. In several of the articles, it was impossible to determine a dose-age relationship as the specific patient ages were not included or patients less than 12 years of age were included. One was an abstract (level 6) of a review of 12 olanzapine ingestions (11 adults and one child) reported to one PC over a 1-year period. Doses ranged from 25 to 135 mg in the adults, and co-ingestants were implicated in seven cases. In the four cases involving patients without co-ingestants, lethargy was reported in three. The lowest dose associated with any effect was not specified (62). Another case series (level 4) of 26 olanzapine-only ingestions in patients older than 16 years reported to one PC over a 5-year period described ingestions of doses ranging from 30 to 830 mg. Clinical effects observed included coma [4], agitation [11],

Table 3. Acute toxicity in patients 12 years of age and older

Drug	Dose	Age (yr)	Mitigating factors	Effect*	Symptom onset†	Confirm. Conc.?‡	Ref. (LOE)
Aripiprazole	Description of 8 aripiprazole ingestions (avg. age 24 years, range 3–43) reported to a PC. Avg. dose was 82 mg. Three of 4 accidental ingestions were watched at home and all of the intentional ingestions were referred to EDs. Two intentional ingestions were admitted for excessive somnolence. All had "favorable outcomes."						41 (4)
	330 mg	27	Also ingested 25 mg of quetiapine	Mod	≤50 min	B (Aripip only)	42 (4)
Clozapine	Description of 150 clozapine ingestions (143 adult and 7 pediatric) reported to the manufacturer or in the literature (some of these cases may therefore appear elsewhere in this summary); doses 50–25,000 mg; some adult patients developed mild to severe clinical effects; lowest dose associated with severe toxicity in an adult was <500 mg.						25 (4)
	Description of 7 clozapine ingestions (ages 22–48 yr); doses 100–16,000 mg; some developed clinical effects ranging from mild to severe; lowest dose associated with mild effects was 100 mg, lowest dose associated with severe toxicity in an adult was 1000 mg.						43 (4)
	100 mg	16	NR	Mod	NR	B	48 (6)
	100 mg	16	Urine positive for THC	Mod	NR	B	48 (6)
	100 mg dissolved in tea	Middle-age	NR	Severe	<2 hr	B	Browne (4)
	800 mg	31	NR	Severe	<1 hr	B	47 (4)
	1000 mg	50	On chronic clozapine	Mod	NR	NR	49 (6)
	Description of 8 clozapine-only ingestions (ages 2–42 yr); doses 1100–5500 mg; >66% developed at least some clinical effects.						26 (4)
	2000 mg	33	? on clozapine chronically	Mod	<20 hr (obtundation ~72 hr)	NR	52 (4)
	~2000 mg	25	Recently started on clozapine; cardiomegaly and left ventricular hypertrophy on autopsy	Death	<3¼ hr	NR	50 (6)
	2250 mg	33	NR	Mod	<2½ hr	B	60 (6)
	3000 mg	26	History of alcoholism, and sleeping problems for which he had been prescribed clozapine	Mod	NR	NR	56 (4)
	3000 mg	29	Also ingested 150 mg zopiclone, alprazolam, and alcohol; possible ingestion of another benzodiazepine	Severe	<1–2 hr	B	44 (4)
	3000–4000 mg	40	On chronic insulin, clozapine, loxapine, and procyclidine	Severe	NR	B	53 (4)
	~3500 mg	20	On chronic flupenthixol, valproate, cloanzepam, and lorazepam; may also have ingested clonazepam	Severe	<6 hr	B	58 (4)
	≤3750 mg	29	History of substance abuse and psychiatric disorders	Severe	≤12–24 hr	B	59 (4)
	5000 mg	19	On chronic clozapine	Mod	~2½ hr	B	45 (4)
	6000–8000 mg	34	On chronic clozapine	Severe	<1 hr	B	51 (4)
	7300 mg	24	On chronic clozapine, moclobemide, and lithium	Severe	<12 hr	NR	54 (4)
	12,500 [~122 mg/kg]	41	On clozapine chronically	Mod	≤42–46 hr	B	55 (4)

(*Continued*)

Table 3. (*Continued*)

Drug	Dose	Age (yr)	Mitigating factors	Effect*	Symptom onset†	Confirm. Conc.?‡	Ref. (LOE)
Olanzapine	Abstract of 12 olanzapine ingestions (11 adults and 1 child); doses 25–135 mg (7 cases had co-ingestants) in the adults; some developed mild–moderate effects.						62 (6)
	Description of 26 olanzapine ingestions (all patients >16 yr); doses 30–830 mg (no co-ingestants); some developed clinical effects ranging from mild to severe; lowest dose associated with mild toxicity was 30 mg; lowest dose associated with moderate toxicity was 120 mg; lowest dose associated with severe toxicity was 560 mg.						61 (4)
	Description of 11 olanzapine-only ingestions (ages 18–33 yr); doses 50–1400 mg; >66% developed at least some clinical effects ranging from mild to severe.						Capel (4)
	75 mg	17	Also ingested prazepam; on prazepam and olanzapine chronically	Mod	NR	NR	68 (6)
	Smoked 20 tablets	24	Also smoked marijuana	Severe	NR	B	78 (6)
	~115 mg	15	History of seizures and depression; either on carbemazepine chronically, or acutely ingested it	Severe	NR	NR	67 (6)
	120 mg	38	On chronic olanzapine	Mild	NR	NR	66 (4)
	150 mg	38	On chronic olanzapine	Severe	<30 min	B	74 (4)
	30 tablets	33	NR	Mod	NR	NR	71 (6)
	200 mg	48	NR	Mod	≤2 hr	NR	67 (6)
	210 mg	12	On chronic olanzapine, paroxetine, and dextroamphetamine/amphetamine	Mod	≤30 min	B	115 (4)
	300 mg	25	On chronic trazadone and olanzapine	Mod	<2 hr	U	72 (6)
	300 mg	33	NR	Mod	NR	U	75 (6)
	350 mg	50	Also ingested alcohol and 70 mg of clonazepam	Mod	<1 hr	B	73 (6)
	Up to 600 mg	31	NR	Severe	NR	B	69 (4)
	As much as 600 mg over ~4 hr	43	Psychiatric problems; cirrhosis; ethanol, diphenhydramine, and trazodone found in blood at autopsy	Death	<10 hr	B (postmortem)	76 (4)
	700 mg	37	Also ingested venlafaxine	Severe	NR	B	63 (4)
	~700 mg	36	On sertraline and olanzapine chronically	Mod	NR	"Quantitative testing"	77 (6)
	~750 mg	62	On chronic olanzapine, lithium, ibuprofen, terazosin, rabeprazole, methocarbamol, and thiamine	Death	NR	B	65 (4)
	800 mg	22	On olanzapine chronically	Mod	~3 hr	B	64 (4)
	1000 mg	44	On olanzapine chronically	Severe	NR	B	74 (4)
	>1000 mg	55	NR	Severe	NR	B	73 (6)
	1110 mg [11.3 mg/kg]	29	NR	Severe	≤1 hr	NR	70 (4)

Quetiapine	Abstract describing 17 adult quetiapine ingestions; doses ≤8000 mg (13 cases had co-ingestants); some developed clinical effects ranging from mild to moderate/severe.						80 (6)
	25 mg	27	Also ingested 330 mg of aripiprazole	Mod	≤50 min	B (Aripip)	42 (4)
	675 mg	45	On chronic quetiapine, carbamazepine, and fluoxetine	Mod (priapism)	The next day	NR	90 (4)
	Prospectively collected data on 18 patients with confirmed quetiapine OD admitted to hospital; doses, when known, 500–24,000 mg; some developed effects ranging from mild to severe effects (12 had co-ingestants); among the 6 patients ingesting quetiapine alone, the minimum dose resulting in any effects was 800 mg, while the minimum dose resulting in seizures/hypotension was 24,000 mg.						79 (2b)
	1000 mg	50	Also ingested ziprasidone 1760 mg	Mod	<1 hr	NR	40 (4)
	1250 mg	15	NR	Mod	<2 hr	B	82 (4)
	1900 mg [26 mg/kg]	14	On mirtazipine and quetiapine chronically	Mod	<30–60 min	NR	88 (4)
	~2000 mg [15.4 mg/kg]	31	On chronic quetiapine, risperidone, clonazepam, topiramate, venlafaxine	Mod	<2 hr	B	81 (4)
	3000 mg	40	On chronic chloral hydrate, valproic acid, quetiapine, and clonazepam	Mod	<1 hr	B	91 (4)
	4700 mg	21	On chronic quetiapine and fluoxetine; also ingested 600 mg fluoxetine	Mod	NR	B	89 (4)
	5400 mg	30	NT	Severe	NT	NT	84 (6)
	Nearly 8000 mg	29	Also ingested ethanol	Severe	≤1 hr	B	93 (6)
	9600 mg	19	NR	Severe	<2 hr	NR	87 (4)
	>10,000 mg	26	NR	Severe	2½ hr	NR	85 (4)
	~10,800 mg	52	Also on chronic felodipine, buspirone, sertraline, quetiapine and IM haloperidol; history of cardiac dysrhythmias and hypertension	Death	NR	B (postmortem)	83 (4)
	12,000 mg	19	On valproic acid and acetaminophen chronically	Severe	<2½ d	B	94 (4)
	~14,000 mg	19	On chronic divalproex, gabapentin, and sertraline	Mod/Severe	≤5 hr	NR	95 (4)
	15,000 mg	36	NR	Severe	NR	NR	86 (6)
	20,000 mg	38	Also ingested 16 g valproate; on quetiapine, valproate, chloridemethyl-diazepam, and venlafaxine chronically	Severe	<4–5 hr	NR	92 (4)

(*Continued*)

Table 3. (*Continued*)

Drug	Dose	Age (yr)	Mitigating factors	Effect*	Symptom onset†	Confirm. Conc.?‡	Ref. (LOE)
Risperidone	Abstract describing 31 risperidone ingestions (adult and pediatric); doses 1–150 mg (15 had co-ingestants); some developed clinical effects ranging from mild to moderate.						38 (6)
	Abstract describing 6 adult risperidone ingestions; doses 5–270 mg (2 had co-ingestants); some developed clinical effects ranging from mild to moderate.						96 (6)
	Letter describing 117 risperidone ingestions; 32 ingested risperdione alone; doses 5–240 mg; some developed clinical effects ranging up to moderate.						97 (6)
	~14 mg [0.3 mg/kg]	34	On risperidone, biperiden, and flunitrazepam chronically	Severe	<1 hr	B	107 (4)
	Description of 10 risperidone-only ingestions (ages 28–63 yr); doses 16–210 mg; <33% developed clinical effects, ranging from mild to moderate						26 (4)
	21 mg [0.41 mg/kg]	16	Also on Provera; prior methylphenidate use	Mod	<30 min	NR	103 (4)
	24 mg [0.41 mg/kg]	16	NR	Mod	~5 min	NR	103 (4)
	40 mg	15	NR	Severe	<1½ hr	NR	102 (4)
	Summary of 31 risperidone ingestions (29 adults/adolescents and 2 children); adult/adolescent doses 21–180 mg (cases with co-ingestants excluded); some developed clinical effects ranging from mild to severe.						35 (4)
	~90 mg [1.2 mg/kg]	45	On risperidone, brotizolam, zopiclone, nitrazepam, haloperidol, and promethazine; possible co-ingestion of other medications	Severe	≤12 hr	B	107 (4)
	100 mg	21	Schizophrenia, on chronic risperidone, paroxetine, and estazolam; possible co-ingestion of paroxetine based on serum conc.	Mod	<4 hr	B	104 (4)
	110 mg [1.7 mg/kg]	15	Also drank wine and smoked marijuana	Mod	<3 hr	B	99 (4)
	120 mg	39	NR	Mod	≤5 hr	NR	100 (4)
	120 mg [1.5 mg/kg]	21	NR	Mod	<2 hr	NR	105 (4)
	228 mg	35	NR	Mod	<20 min	NR	106 (4)
	240 mg	29	NR	Mod	<45 min	NR	98 (4)
	270 mg	41	On risperidone chronically; intermittent benzodiazepine use	Severe	≤3 hr	NR	101 (4)
	≤403 mg	45	Schizophrenic; possible ingestion of buspirone	Death	NR	B (postmortem)	108 (4)

Ziprasidone	Description of 30 ziprasidone ingestions (avg. age 23 yr, range 1–41) reported to a PC. Avg. dose was 206 mg. 7 of 8 accidental ingestions were watched at home; all of the intentional ingestions were referred to EDs. One patient ingested an unknown dose and presented comatose, required intubation, and recovered after 8 hours. All others had "good outcomes."						41 (6)
	Abstract describing 7 pediatric ziprasadone-only ingestions (5 were 10–16 yr old); doses 60–360 mg; some developed clinical effects ranging from mild to moderate.						39 (6)
	Abstract describing 26 adult ziprasadone-only ingestions; doses 180–4020 mg were reported; some developed clinical effects ranging from mild to severe						109 (6)
	1040 mg	50	? on ziprasadone chronically	Mod (QTc prolongation)	6–10 hr	NR	22 (6)
	1200 mg	37	Also ingested heroin and cocaine; urine toxicology positive for opiates, benzodiazepines and methadone	Mod	<4 hr	NR	40 (4)
	1760 mg	50	Also ingested quetiapine 1000 mg	Mod	<1 hr	NR	40 (4)
	3120 mg	50	NR	Mod	<4½ hr	NR	110 (4)
	4020 mg	38	On chronic quetiapine, gabapentin, venlafaxine, metformin, rofecoxib, pravastatin	Mod/Severe	<6 hr	NR	111 (4)

**Mild* = local effects only or mild systemic effects (e.g., sedated but arousable, agitated); *mod* = systemic effects (e.g., more severe sedation or agitation, tachycardia, hypertension, hyperthermia, ECG abnormalities); *severe* = life-threatening systemic effects (e.g., severe hyperthermia or rigidity, coma or sedation requiring intubation, seizures, respiratory depression, hypotension, dysrhythmias).
†maximal time of onset; (i.e., symptoms were present on admission, but might have begun earlier).
‡*B* = blood, *U* = urine.
NR = not reported or none reported.
NT = not fully translated.

alternating agitation and somnolence [9], seizures [1], tachycardia [8], hypotension [2], miosis [8], and ECG changes (QTc prolongation, PVCs, T-wave elevation) [3]. The lowest dose associated with mild toxicity was 30 mg; the lowest dose associated with moderate toxicity was 120 mg; and the lowest dose associated with severe toxicity was 560 mg (61). There were also 17 level 4 and 6 articles with individual case information on 25 acute olanzapine ingestions in patients 12 years of age and older (63–78).

The package insert for Zyprexa indicates that 67 of 3100 patients involved in premarketing trial overdosed on olanzapine. The largest ingested dose was 300 mg, which resulted in drowsiness and slurred speech (6).

Quetiapine

One level 2b article presented data on 18 patients with confirmed quetiapine overdose admitted to one toxicology service over a 1-year period. While the data collection was prospective, the estimation of dose was retrospective and, thus, subject to questions of accuracy. Doses, when known, ranged from 500 to 24,000 mg. In this series, six patients ingested quetiapine alone. The following clinical effects were observed in those patients: seizures [1], CNS and respiratory depression [2], delirium [3], hypotension [1], and tachycardia [6]. Among the six patients ingesting only quetiapine, the minimum dose resulting in any effect was 800 mg. In this subgroup, a 2.4-g dose resulted in seizures and hypotension (79). There was also an abstract (level 6) of a 3-year review of 17 intentional quetiapine ingestions in adults reported to one PC; 13 involved co-ingestants. The maximum dose reported in this series was 8 g. In the four cases that involved quetiapine alone, the following clinical effects were reported: agitation [1], tachycardia [3], sedation [2], premature ventricular contractions [2], and QRS prolongation [1] (80). There were also 17 level 4 or 6 articles with individual case information on acute quetiapine ingestions in patients 14–52 years of age (40,42,81–95). The lowest dose of quetiapine associated with any toxicity was the case of a 27-year-old woman who ingested 25 mg and developed moderate effects. However, she had also ingested 330 mg of aripiprazole (42). A 15-year-old girl developed lethargy, slurred speech, agitation, tachycardia, hypotension, and miosis after ingesting 1250 mg of quetiapine (82). The lowest dose associated with severe toxicity was 5400 mg in a 30-year-old woman. She developed stupor, seizures, hypotension, tachycardia, QRS prolongation, and ST segment changes (84).

The package insert for Seroquel indicates that patients have survived acute overdoses of up to 30 g quetiapine and that a clinical trial patient died after ingesting 13.6 g of quetiapine alone. Ingestion of 9600 mg in another patient resulted in hypokalemia and first-degree heart block (7).

Risperidone

There were no level 1–3 articles with dose-toxicity information for risperidone. However, there were five level 4 or 6 reports that included patients 12 years of age and older with acute risperidone exposure from which some dose-toxicity information could be extracted (26,35,38,96,97). A case series (level 4) described 31 risperidone ingestions reported to a PC over 13 months. Risperidone was the only drug ingested by 14 adults/adolescents, three of whom remained asymptomatic (doses 3–42 mg). Symptoms in the others included lethargy [7], tachycardia [6], spasm/dystonia [3], hypotension [2], and dysrhythmia [2] (35). An abstract (level 6) reviewed another 31 risperidone ingestions (adult and pediatric) reported to a different PC over a 15-month period. Reported doses ranged from 1 to 150 mg. Sixteen of the cases involved risperidone alone, and five of these patients were reported to be asymptomatic. In the remaining 11 patients who ingested risperidone alone, the following clinical effects were reported: lethargy [8], tachycardia [2], and vomiting [1] (38). Another abstract described risperidone ingestions by six adults reported to a PC. Doses ranged from 5 to 270 mg. Two cases included chlordiazepoxide and naproxen as co-ingestants. Clinical effects reported included slurred speech [2], drowsiness [3], altered level of consciousness [1], tremors [1], agitation [1], extrapyramidal effects [1], tachycardia [3], and hypertension [1] (96). There were also 13 cases reported in 11 level 4 or 6 articles (98–108). The lowest dose associated with severe toxicity was approximately 14 mg in a 34-year-old woman who became comatose and developed bradycardia (107).

The Risperdal package insert mentions eight nonfatal overdoses in premarketing studies with doses ranging fro 20 to 300 mg. Postmarketing experience includes overdoses up to 360 mg; the most commonly reported clinical effects have been sedation, tachycardia, hypotension, and extrapyramidal effects (8).

Ziprasidone

There were no level 1–3 articles with dose-toxicity information for ziprasidone. However, there was one case series and two level 6 abstracts of case series that included patients 12 years of age and older with acute ziprasidone ingestions and from which some information could be obtained. A case series (level 4) briefly described 30 ziprasidone ingestions reported to a PC. The mean dose ingested was 206 mg; no range was provided. Patients ranged in age from 1 to 43 years (mean 23 years). Of the eight accidental ingestions, seven were observed at home and the eighth was seen at an emergency department and discharged "without incident." Almost all (19/22) of the intentional ingestion patients were evaluated at emergency departments with one presenting comatose and requiring intubation but recovered after 8 hours. The age of this patient was not provided and the dose ingested was stated to be unknown (41). The first abstract was a review of 26 adult ziprasidone-only ingestions reported to a PC during a year. In this series, doses ranged from 180 to 4020 mg. The clinical effects reported were somnolence [19], tachycardia [8], and hypotension [1] (39). The second abstract was a

review of seven pediatric ziprasidone-only ingestions reported to a PC over a 1-year period. For this series, ingested dose ranged from 60 to 360 mg. Five of the seven cases involved children from 6 to 16 years of age; two of the five patients were asymptomatic. The three remaining patients were somnolent, and there was one report of tachycardia (109).

There were four level 4 or 6 articles with information regarding acute ziprasidone ingestions in five patients 12 years of age and older (22,40,110,111). The lowest dose associated with moderate to severe toxicity was 4020 mg ingested by a 38-year-old woman who developed fluctuating mental status, hypotension, QRS prolongation, diarrhea, and urinary retention (111).

The package insert for Geodon indicates that there were 10 overdoses among more than 5400 patients in premarketing trials. One patient ingested 3240 mg with only minimal sedation, slurred speech, and transient hypertension (9).

Onset of effects

In order to guide decisions about out-of-hospital transportation and management, the expert consensus panel members investigated the time of symptom onset after atypical antipsychotic exposures. All articles with reports of toxicity were searched for evidence documenting or estimating a time of onset. Unfortunately, the vast majority of articles reported times of presentation to healthcare facilities but not times of symptom development, which might have occurred earlier, later, or not at all. Thus, in most cases, it was only possible to establish an upper limit of time to onset. In only a few reports was an exact time of onset known and reported.

In addition, there were too few data to separate time of onset by patient age. Similarly, there were insufficient data to detect any difference in onset of effects between individual antipsychotic agents.

Onset of effects after acute overdose

In discussing the onset of effects after atypical antipsychotic ingestion, care must be taken to distinguish the initial onset of effects from the onset of serious or major effects and to distinguish the time to peak effects as compared to the time of delayed effects or later deterioration. Furthermore, decontamination measures utilized might have differed between the patients described in the included articles. In essentially all of these studies reviewed, it was not clear whether, or what, symptoms were present before the late-occurring events.

In most cases, the onset of initial effects after atypical antipsychotic ingestion was within a few hours. There was only one case report that reported the occurrence of significant clinical effects, without any prior signs or symptoms, beyond 4 hours after ingestion of the atypical antipsychotic. This was an abstract (level 6) describing a 51-year-old man who ingested 1040 mg of ziprasidone and had a normal ECG at 6 hours after ingestion but had an ECG with QTc prolongation 4 hours later. The presence or absence of other effects was not noted in the abstract (22). There were also several level 4 or 6 reports of patients who presented to healthcare facilities 12 hours to 2½ days after ingestion, at which time they were noted to have toxicity (21,27,30,354,55,64,94). However, in all of these cases, it was unclear when the signs of toxicity actually began. There was also a level 4 case report of a 33-year-old woman who presented initially with hypertension and tachycardia after an ingestion of 2000 mg clozapine but became obtunded at 72 hours after ingestion (52).

A number of patients in level 4 or 6 case reports were noted to deteriorate after presentation at healthcare facilities. In some cases, this deterioration was relatively rapid (85), but in most cases it occurred over the course of hours or days (30,31,52,65,68,79,87,101).

Potential out-of-hospital management

Decontamination Measures

Decontamination measures reported in the literature included activated charcoal, ipecac syrup, gastric lavage, and various cathartics. Most of these measures had too little evidence to comment on their effectiveness, and others are not likely to be available in an out-of-hospital setting. Only decontamination measures that could reasonably be expected to be available and carried out in an out-of-hospital setting and for which evidence was available regarding their use are reviewed in this summary.

Activated charcoal

There were no level 1–3 studies that investigated the efficacy or effectiveness of activated charcoal in adsorbing atypical antipsychotic medications. There were numerous level 4 or 6 case reports or series that described administration of single or multiple doses of activated charcoal to patients with atypical antipsychotic overdose (22,23,25,26,28,29,31,33,37,39,40,42–45,47,48,52,54–56,58–62,64,67,69,70,72,78–82,84,87–89,91,92,95,96,98–103,105–107,109–116). However, it was impossible to determine the effectiveness of activated charcoal from these reports given the lack of any controls, the concurrent use of other therapies, and the fact that activated charcoal does not produce immediate clinical improvement (i.e., outcome is generally measured by improved kinetic parameters or the prevention of later clinical sequelae).

The package insert for Abilify states that the administration of 50 g activated charcoal 1 hour after ingestion of a single 15-mg dose of aripiprazole reduced absorption by about 50% (3). Similarly, the package insert for Zyprexa states that 1 g of activated charcoal given at an unspecified time reduced the absorption of an unstated dose of olanzapine by about 60% (6). These data are encouraging, but the absence of study detail means they should be interpreted cautiously.

Ipecac syrup

There were no controlled studies of ipecac syrup use in the treatment of atypical antipsychotic overdose, nor were there any volunteer studies examining the effectiveness of ipecac syrup in reducing atypical antipsychotic absorption, even after therapeutic doses. There was one case report and two case series (level 4) in which ipecac syrup was administered after atypical antipsychotic overdose or suspected overdose (33,80,96). In the case report, the child became drowsy subsequent to ipecac syrup administration (33). None of these authors described development of aspiration pneumonia associated with ipecac syrup use. These reports were uncontrolled and it is impossible to draw any conclusions about ipecac syrup's effectiveness or its risk-benefit ratio.

Specific treatment measures

The reviewed literature reported a variety of treatment measures that had been used for atypical antipsychotic toxicity/overdose. Most of the treatments had too little evidence available to comment on their effectiveness. There were no prospective or retrospective controlled data in the out-of-hospital or the in-hospital setting for any of the treatment measures. Only those measures that anecdotally appeared to provide temporal improvement, based on individual case reports, case series, or their abstracts (level 4 or 6) that might reasonably be available in the out-of-hospital setting are mentioned here. Sodium bicarbonate was used in two case reports of patients with increased QRS durations after ingestions of olanzapine or quetiapine. One of these was suspected to have co-ingested a tricyclic antidepressant. In both cases, there was a temporal association between sodium bicarbonate administration and QRS narrowing (67,93). Diphenhydramine was reported to improve various symptoms related to dopaminergic blockade in a number of patients with atypical antipsychotic toxicity (22,28,37,72,96). In one case, muscle rigidity improved (28) and lethargy, drooling, and flaccidity resolved in another (22). In one case it was reported to be ineffective (36).

There were also a number of general supportive measures reported in the atypical antipsychotic literature including oxygen, intubation and ventilation, CPR, IV fluids, anticonvulsants, vasopressors, antiarrhythmics, dextrose, cooling measures, treatment of allergic reactions, and others. Since none of these had controlled data to support their effectiveness in atypical antipsychotic toxicity, and since they are already routinely used in the out-of-hospital setting or are not available in such a setting, the anecdotal reports are not presented here. The package inserts for Zyprexa, Seroquel, Risperdal, and Geodon caution against the use of epinephrine, dopamine, and other sympathomimetics with ß-agonist activity since their use might worsen hypotension resulting from the drugs' α-adrenergic blocking properties. No specific data are provided to support these statements, so it is unclear if they are based on only theoretical considerations or actual patient experience (6–9).

Type of healthcare facility, mode of transportation, and initial treatment

There were no studies that addressed the type of healthcare facility to which patients should be referred or how they should be transported. The expert consensus panel concluded that patients should be referred to emergency departments that have the ability to assess and manage the effects of atypical antipsychotic medications in a timely manner. Any patient already experiencing any signs or symptoms, other than mild drowsiness, thought to be related to medication toxicity should be should be transported to an emergency department regardless of the dose ingested. Transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department. For symptomatic patients, initial care should include airway management, vital sign monitoring, and continuous cardiac monitoring. A single dose of activated charcoal can be administered in the out-of-hospital setting if less than 1 hour has elapsed since the ingestion, the patient is able to control his airway, local protocols support out-of-hospital activated charcoal administration, and activated charcoal administration will not delay transportation to an emergency department. Given the risk of sedation, ipecac syrup administration is contraindicated. Hypotensive patients should be treated with intravenous fluids. Intravenous vasopressors should be considered for patients with hypotension who do not respond to fluids.

Conclusions

The expert consensus panel chose to emphasize the importance of information that would be needed in order to make a sound triage decision for the patient with the ingestion of an atypical antipsychotic medication. These variables include the patient's intent, the patient's symptoms, the product and dose ingested, and the expected time of symptom onset. The panel agreed that in each case, the judgment of the specialist in poison information, the poison center medical director, or other poison center-affiliated clinicians might override any specific recommendation from this guideline.

Patient intent

The panel concluded that all patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g., child abuse or neglect) should be referred to an emergency department. Patients without these characteristics are candidates for consideration of out-of-hospital management of their ingestion.

Symptoms

There were a number of articles reporting adverse effects occurring with "therapeutic" doses of atypical antipsychotic medications that are primarily mild to moderate in nature. Furthermore, it is likely that there are many other such articles that were not identified or recovered, and therefore not reviewed for this guideline, simply because of the search criteria used to identify articles. The panel concluded that any patient demonstrating clinical manifestations beyond mild drowsiness (aroused with speaking voice or light touch), regardless of the dose ingested, should be referred for emergency department evaluation. The expert consensus panel concluded that these triage guidelines could be used when a capable, adult caretaker is available to monitor the patient. Consideration should be given to the time of day that home observation will take place, since observation during normal sleep hours might not be practical or reliable.

Dose

There is little information in the literature to adequately define a minimum acute toxic dose of any atypical antipsychotic medication. Several reviews that included summary data have concluded that the atypical antipsychotic medications as a class have a wide margin of safety, especially when compared to phenothiazine-type and butyrophenone antipsychotics. None of these medications are FDA-approved for pediatric use. However, randomized controlled trials that included children have been conducted with clozapine, olanzapine, risperidone, and ziprasidone (1,117–135). Similar trials have not been conducted with aripiprazole and quetiapine. Given the difficulty extrapolating clinical trials data to cases involving acute toxicity and the lack of evidence for some agents, the panel concluded that emergency department referral should be based primarily upon the presence of signs and symptoms. The panel concluded that patients less than 12 years of age who are naïve to atypical antipsychotic medications and are experiencing no more than mild clinical effects can be observed at home unless they have ingested a dose that is equal to or more than the lowest reported acute dose that resulted in at least moderate toxicity or four times the initial adult dose, whichever dose is smaller (i.e., aripiprazole 15 mg, clozapine 50 mg, olanzapine 10 mg, quetiapine 100 mg, risperidone 1 mg, ziprasidone 80 mg). Patients 12 years of age and older who are naïve to atypical antipsychotic medications and are experiencing no more than mild clinical effects can be observed at home unless they have ingested more than five times the initial adult dose for the implicated antipsychotic medication (i.e., aripiprazole 50 mg, clozapine 62.5 mg, olanzapine 25 mg, quetiapine 125 mg, risperidone 5 mg, ziprasidone 100 mg). The panel concluded that patients who use atypical antipsychotic medications on a chronic basis can be observed at home if they have acutely ingested no more than five times their personal single therapeutic dose (not daily dose) of the implicated antipsychotic medication. Patients exceeding these dose limits or demonstrating clinical manifestations beyond mild drowsiness, regardless of the dose ingested, should be referred for emergency department evaluation.

Time to onset of toxicity

There is limited information in the literature to adequately define a minimum or a maximum time of onset of toxicity for any specific atypical antipsychotic. Based on the available cases, the expert consensus panel concluded that patients who have unintentional atypical antipsychotic ingestions and were asymptomatic or had only mild drowsiness in the 6 hours following the ingestion could stay at home with poison center follow-up, since the likelihood of delayed toxicity is small. Consideration should be given to the time of day that home observation will take place, since observation during normal sleep hours might not be practical or reliable.

Healthcare facility, transportation, and initial treatment

There were no studies that addressed the type of healthcare facility to which patients should be referred or how they should be transported. The expert consensus panel concluded that patients should be referred to emergency departments that have the ability to assess and manage the effects of atypical antipsychotic medications in a timely manner. Any patient already experiencing any signs or symptoms, other than mild drowsiness, thought to be related to medication toxicity should be should be transported to an emergency department regardless of the dose ingested. Transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department. For symptomatic patients, initial care should include airway management, vital sign monitoring, and continuous cardiac monitoring. A single dose of activated charcoal can be administered in the out-of-hospital setting if less than 1 hour has elapsed since the ingestion, the patient is able to control his/her airway, local protocols support out-of-hospital activated charcoal administration, and activated charcoal administration will not delay transportation to an emergency department. Given the risk of sedation, ipecac syrup administration is contraindicated. Hypotensive patients should be treated with intravenous fluids. Intravenous vasopressors should be considered for patients with hypotension who do not respond to fluids.

Recommendations

These recommendations are provided in chronological order of likely clinical use. The grade of recommendation appears in parentheses.

1. Patients with stated or suspected self-harm or the recipient of a potentially malicious administration of an atypical antipsychotic medication should be referred to an emergency department immediately. This activity should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (Grade D).
2. Patients without evidence of self-harm should have further evaluation, including determination of the precise dose ingested, presence of signs or symptoms of toxicity, history of other medical conditions, and the presence of co-ingestants (Grade C).
3. Asymptomatic patients without evidence of attempted self-harm are unlikely to develop symptoms if the interval between the ingestion and the call is greater than 6 hours. These patients do not need referral and should receive follow-up based on local poison center protocols (Grade C).
4. All patients less than 12 years of age who are naïve to atypical antipsychotic medications and are experiencing no more than mild drowsiness (lightly sedated and can be aroused with speaking voice or light touch) can be observed at home unless they have ingested more than four times the initial adult dose for the implicated antipsychotic medication or a dose that is equal to or more than the lowest reported acute dose that resulted in at least moderate toxicity, whichever dose is smaller (i.e., aripiprazole 15 mg, clozapine 50 mg, olanzapine 10 mg, quetiapine 100 mg, risperidone 1 mg, ziprasidone 80 mg) (Grade D).
5. All patients 12 years of age or older who are naïve to atypical antipsychotic medications and are experiencing no more than mild drowsiness can be observed at home unless they have ingested more than five times the initial adult dose for the implicated antipsychotic medication (i.e., aripiprazole 50 mg, clozapine 62.5 mg, olanzapine 25 mg, quetiapine 125 mg, risperidone 5 mg, ziprasidone 100 mg) (Grade D).
6. Patients who use atypical antipsychotic medications on a chronic basis can be observed at home unless they have acutely ingested more than 5 times their current single dose (not daily dose) of the implicated antipsychotic medication (Grade C).
7. Patients who have ingested less than a threshold dose (see Recommendations 4–6) and are exhibiting no more than mild drowsiness can be observed at home with instructions to call the poison center if symptoms develop or worsen. If mild drowsiness is present at the time of the initial call, the poison center should make follow-up calls until at least 6 hours after ingestion. Consideration should be given to the time of day that home observation will take place. Observation during normal sleep hours might not be reliable. Depending on local poison center policy, patients could be referred to an emergency department if the observation would take place during normal sleeping hours of the patient or caretaker (Grade D).
8. Any patient already experiencing any signs or symptoms, other than mild drowsiness, thought to be related to atypical antipsychotic medication toxicity should be transported to an emergency department. Transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department (Grade D).
9. Do not induce emesis (Grade D).
10. There are no specific data to suggest benefit from out-of-hospital administration of activated charcoal in patients exposed to atypical antipsychotic medications. Poison centers should follow local protocols and experience with the out-of-hospital use of activated charcoal in this context. Do not delay transportation in order to administer charcoal (Grade D).
11. For patients who merit evaluation in an emergency department, transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department. Continuous cardiac monitoring should be implemented given reports of conduction disturbances associated with this class of medications. Provide usual supportive care en route to the hospital, including airway management and intravenous fluids for hypotension (Grade D).
12. Depending on the specific circumstances, follow-up calls should be made to determine outcome at appropriate intervals based on the clinical judgment of the poison center staff (Grade D).

Implications for research

The panel identified the following topics where additional research is needed or analysis of existing databases might be useful.

1. A large-scale, prospective, rigorous study of unintentional atypical antipsychotic medication poisonings, stratified by implicated agent, should be undertaken. This study should consider numerous factors including confirmation of the estimated dose ingested, the presence or absence of underlying illnesses, the use of other medications, the presence or absence of symptoms, changes in ECG findings, the times of onset of any toxicity, the duration of medical observation, and outcomes. Given the low incidence of serious toxicity after unintentional ingestion, especially in children, a multicenter and multi-year study will be needed.
2. Epidemiologic analyses of large data bases (e.g., TESS) should be undertaken to better characterize the toxicities of atypical antipsychotic medications.
3. Efficacy and safety studies are also required to better characterize the role of sodium bicarbonate as an adjunctive therapeutic agent in the care of patients who experience cardiovascular toxicities from atypical antipsychotic medications.

4. The effectiveness and safety of out-of-hospital activated charcoal use in patients with poisoning from atypical antipsychotics need to be better characterized.

Disclosures

Dr. Erdman was an employee of AstraZeneca at the time of his work on this guideline and Dr. Booze's husband is employed by AstraZeneca. There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

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Appendix 1

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Appendix 2

Grades of recommendation and levels of evidence

Grade of recommendation	Level of evidence	Description of study design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	"Outcomes" research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research
Z	6	Abstracts

Appendix 3

Secondary review panel organizations

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Pharmacists Association
American Public Health Association
American Society of Health-System Pharmacists
Association of Maternal and Child Health Programs
Association of Occupational and Environmental Clinics
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centres
Centers for Disease Control and Prevention – National Center for Injury Prevention and Control
Consumer Federation of America
Consumer Product Safety Commission

Department of Transportation
Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of Emergency Medical Technicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

Appendix 4

Triage algorithm for atypical antipsychotic poisoning

Is suicidal, abuse, or malicious intent suspected?	YES → Refer to emergency department.	
NO ↓		
Is the home situation of concern? (e.g., patient lives alone or family/caregiver seems unreliable)	YES → Refer to emergency department.	
NO ↓		
Is the patient manifesting more than mild drowsiness?*	YES → Refer to emergency department.	
NO ↓		
Have more than 6 hours passed since the ingestion and has the patient remained asymptomatic or experienced only mild drowsiness*?	YES → Toxicity unlikely to occur. No referral or treatment is needed.	
NO ↓		
Is the patient <12 y.o. and therapeutically naïve to the atypical antipsychotic that was unintentionally taken in overdose?	YES → Did they ingest more than the following amount of an individual atypical antipsychotic (4 times an adult initial therapeutic dose or a dose that is more than or equal to the lowest reported acute dose that resulted in at least moderate toxicity, whichever is smaller)? aripiprazole 15 mg clozapine 50 mg olanzapine 10 mg quetiapine 100 mg risperidone 1 mg ziprasidone 80 mg	YES → Refer to emergency department.
NO ↓	↙NO	
Is the patient ≥12 y.o. and therapeutically naïve to the atypical antipsychotic that was unintentionally taken in overdose?	YES → Did they ingest more than the following amount (5 times an adult initial therapeutic dose)? aripiprazole 50 mg clozapine 62.5 mg olanzapine 25 mg quetiapine 125 mg risperidone 5 mg ziprasidone 100 mg	YES → Refer to emergency department.
NO ↓	↙NO	
Is the patient chronically taking an atypical antipsychotic medication?	YES → Have they ingested more than 5 times their current single dose (not daily dose)?	YES → Refer to emergency department.

Is suicidal, abuse, or malicious intent suspected?

YES → Refer to emergency department.

NO ↓

↙ NO

Observe at home. Instruct caller to call poison center back if symptoms appear. Consider poison center-initiated follow-up within 6 hours of initial call. Refer to an emergency department should symptoms beyond mild drowsiness develop. Check for drug interactions and act accordingly, particularly if the potential for adverse consequences is severe.

*For the purposes of this guideline, mild drowsiness is defined as lightly sedated and can be aroused with speaking voice or light touch.