



## Complete Summary

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### GUIDELINE TITLE

Atypical antipsychotic medication poisoning: an evidence-based consensus guideline for out-of-hospital management.

### BIBLIOGRAPHIC SOURCE(S)

Cobaugh DJ, Erdman AR, Booze LL, Scharman EJ, Christianson G, Manoguerra AS, Caravati EM, Chyka PA, Woolf AD, Nelson LS, Troutman WG. Atypical antipsychotic medication poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 Dec;45(8):918-42. [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

Atypical antipsychotic medication poisoning

#### Note:

- 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 does not provide guidance on exposures to typical antipsychotics, such as phenothiazines and butyrophenones, which have different pharmacological effects and toxicity profiles.
- 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.

### **GUIDELINE CATEGORY**

Evaluation  
Management  
Risk Assessment

### **CLINICAL SPECIALTY**

Emergency Medicine  
Family Practice  
Internal Medicine  
Pediatrics

### **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Emergency Medical Technicians/Paramedics  
Nurses  
Pharmacists  
Physicians

### **GUIDELINE OBJECTIVE(S)**

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:

- Describing the process by which an ingestion of an atypical antipsychotic medication might be evaluated.
- Identifying the key decision elements in managing cases of atypical antipsychotic medication ingestion.
- Providing clear and practical recommendations that reflect the current state of knowledge.
- Identifying needs for research.

### **TARGET POPULATION**

Adults and children with suspected atypical antipsychotic medication poisoning

### **INTERVENTIONS AND PRACTICES CONSIDERED**

**Evaluation**

1. Assessment of key decision elements for triage
  - Patient intent
  - Patient's age
  - Dose of the ingested product
  - Patient's symptoms
  - Time to onset of toxicity
  - History of other medical conditions and presence of co-ingestants

## **Management**

1. Referral to an emergency department, including transportation via ambulance
2. Airway management, vital sign monitoring, and continuous cardiac monitoring
3. Activated charcoal administration
4. Intravenous fluids and intravenous vasopressors for hypotension
5. Home observation
6. Follow-up

**Note:** Emesis induction was considered but not recommended.

## **MAJOR OUTCOMES CONSIDERED**

- Signs and symptoms of toxicity
- Mortality
- Dose required for the development of toxicity

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

#### **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 Medical Subject Headings (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 0–23 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 unintentional 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).

### **NUMBER OF SOURCE DOCUMENTS**

Not stated

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

<b>Level of Evidence</b>	<b>Description of Study Design</b>
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.)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality randomized clinical trial)
2c	"Outcomes" research

<b>Level of Evidence</b>	<b>Description of Study Design</b>
3a	Systemic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series, single case reports (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research
6	Abstracts

## **METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review with Evidence Tables

### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

#### **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, efficacy 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, electrocardiogram [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 American Association of Poison Control Centers (AAPCC) website.

### **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus (Delphi)

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

An expert consensus panel was established to develop the guideline (see Appendix 1 of the original guideline document). 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 U.S. 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.

### **Guideline Writing and Review**

A guideline draft was prepared by the lead author. 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.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

The rating scheme for the strength of the recommendation (A-D, Z) is directly tied to the level of evidence supporting the recommendation.

<b>Grade of Recommendation</b>	<b>Level of Evidence</b>
A	1a
	1b
	1c
B	2a
	2b
	2c
	3a
	3b
C	4
D	5
Z	6

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (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 (see Appendix 3 of the original guideline document). 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.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Grades of recommendation (A-D, Z) and levels of evidence (1a-6) are defined at the end of the "Major Recommendations" field.

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 to 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 in to the 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)**.

**Definitions:**

**Grades of Recommendation and Levels of Evidence**

<b>Grade of Recommendation</b>	<b>Level of Evidence</b>	<b>Description of Study Design</b>
A	1a	Systematic review (with homogeneity) of randomized clinical trials

Grade of Recommendation	Level of Evidence	Description of Study Design
	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

### CLINICAL ALGORITHM(S)

An algorithm is provided in Appendix 4 of the original guideline document for triage for atypical antipsychotic poisoning.

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate out-of-hospital triage and management of patients with suspected atypical antipsychotic medication poisoning

### POTENTIAL HARMS

Not stated

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Given the risk of sedation, ipecac syrup administration is contraindicated.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the United States. 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.
- 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.

### Limitations of the Published Data

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 is unclear. Retrospective data from case reports or case series were often confounded by concomitant exposure 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.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Clinical Algorithm

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better

### IOM DOMAIN

Effectiveness  
Timeliness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Cobaugh DJ, Erdman AR, Booze LL, Scharman EJ, Christianson G, Manoguerra AS, Caravati EM, Chyka PA, Woolf AD, Nelson LS, Troutman WG. Atypical antipsychotic medication poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 Dec;45(8):918-42. [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2007 Aug 6

### GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

### SOURCE(S) OF FUNDING

Health Resources and Services Administration, U.S. Department of Health and Human Services

### GUIDELINE COMMITTEE

Not stated

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

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.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [American Association of Poison Control Centers](#).

Print copies: Available from the American Association of Poison Control Centers, 3201 New Mexico Avenue NW, Suite 330, Washington, DC 20016

## **AVAILABILITY OF COMPANION DOCUMENTS**

None available

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI Institute on December 17, 2007. The information was verified by the guideline developer on January 14, 2008.

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