Complete Summary

GUIDELINE TITLE

Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Woolf AD, Erdman AR, Nelson LS, Caravati EM, Cobaugh DJ, Booze LL, Wax PM, Manoguerra AS, Scharman EJ, Olson KR, Chyka PA, Christianson G, Troutman WG, American Association of Poison Control Centers. Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007;45(3):203-33. [311 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Tricyclic antidepressant poisoning

Note: This guideline does not provide guidance on exposures to some antidepressants such as maprotiline, amoxapine, and loxapine, which are heterocyclic compounds with somewhat different adverse effect profiles. Dothiepin, dibenzepin, melipramine, prothiaden (dosulepin), and other antidepressants not currently available in the U.S. are not included in this guideline.

This guideline applies to ingestion of tricyclic antidepressants alone. Co-ingestion of additional substances could require different referral and management recommendations depending on their combined toxicities.

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)

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial out-of-hospital management of patients with a suspected exposure to tricyclic antidepressants by:

- Describing the manner in which an ingestion of a tricyclic antidepressant might be managed
- Identifying the key decision elements in managing cases of tricyclic antidepressant ingestion
- Providing clear and practical recommendations that reflect the current state of knowledge
- Identifying needs for research

TARGET POPULATION

Adults and children with suspected exposures to tricyclic antidepressants

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision points for triage:
    - Patient intent
    - Route of exposure and estimated dose
    - Time since exposure and symptoms
    - Pattern of ingestion (acute or chronic)
    - Assessment of symptoms
    - Presence of co-ingestants

- Assessment of any underlying exacerbating conditions, such as convulsions or cardiac arrhythmias

Management

1. Referral to an emergency department, including transport by emergency medical services and close monitoring, as warranted
2. Prehospital administration of activated charcoal
3. Follow-up calls to determine the outcome for tricyclic antidepressant (TCA) ingestion
4. Electrocardiogram or rhythm strip assessment
5. Prehospital interventions, such as intravenous fluids, cardiovascular agents, and respiratory support
6. Sodium bicarbonate
7. Benzodiazepines (for TCA-associated convulsions)

Note: Interventions and practices considered but not recommended include induction of emesis, flumazenil.

MAJOR OUTCOMES CONSIDERED

- Mortality
- The threshold dose for the development of toxicity following tricyclic antidepressant ingestion
- Signs and symptoms 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

Search Strategy

The National Library of Medicine's MEDLINE database was searched (1966 to September 2003) using antidepressive agents, tricyclic as a Medical Subject Heading (MeSH) term with the subheadings poisoning (po) or toxicity (to), limited to humans. MEDLINE and PreMEDLINE (1966 to September 2003) were searched using amitriptyline, nortriptyline, imipramine, desipramine, protriptyline, clomipramine, and doxepin as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdose* or toxic*, limited to humans. This process was repeated in International Pharmaceutical Abstracts (1970 to September 2003, excluding meeting abstracts), Science Citation Index (1977 to September 2003), Database of Abstracts of Reviews of Effects (accessed September 2003), Cochrane Database of Systematic Reviews (accessed September 2003), and Cochrane Central Register of Controlled Trials (accessed September 2003).

The bibliography of the tricyclic antidepressant (TCA) management in Poisindex was examined and the abstracts of suitable articles not previously discovered by the search were reviewed. The bibliographies of recovered articles were reviewed to identify previously undiscovered articles. In addition, the chapter bibliographies in five current major pharmacology and toxicology textbooks were reviewed for additional articles with original human data. Published abstracts on TCA overdose presented at the North American Congress of Clinical Toxicology between the years 1995 to 2004 were also reviewed.

Criteria Used to Identify Applicable Studies

Published studies that provided original information on the epidemiology, pharmacology, toxicology, toxic dose, decision-making, or management of TCA poisoning were included. Animal studies were not systematically reviewed for the guideline. Reviews, letters to the editor, commentaries, and published information that did not contribute original data were excluded.

Article Selection

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, looking specifically for those that dealt with 1) estimations of ingested doses with or without subsequent signs or symptoms, and 2) management techniques that might be suitable for out of- hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that did not meet either of the preceding criteria, did not add new data (e.g., reviews with few references, editorials), or clearly described only inpatient procedures (e.g., hemodialysis) or forensic analyses without exposure details.

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

Levels of Evidence

Level of Evidence	Description of Study Design
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

Level of Evidence	Description of Study Design
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
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 retrieved from the original search were reviewed by a single, trained, physician abstractor. Each article was assigned a level-of-evidence score from 1 to 6 using the rating scheme developed by the Centre for Evidence-based Medicine at Oxford University (see "Rating Scheme for the Strength of the Evidence" field). Single case reports were classified along with case series as level 4. The complete paper was then reviewed for original human data regarding the toxic effects of cyclic antidepressants, or original human data directly relevant to the out-of-hospital management of patients with cyclic antidepressant-related 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. This full evidence table is available at http://www.aapcc.org/DiscGuidelines/Guidelines%20Tables/TCA%20Evidence%20Table.pdf. The completed table of all abstracted articles was then forwarded to the guideline primary author and panel members for review and consideration in developing the guideline. A list of foreign articles for which English translations were not available and a list of articles that could not be located were also forwarded to the guideline primary author for a decision on whether the article merited translation and inclusion in the guideline. Every attempt was made to locate such 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. In addition to the complete evidence table of all the abstracted articles, several brief summary tables were generated to highlight the available data for various relevant subpopulations (e.g., acute pediatric ingestions). These summary tables were also forwarded to the author and guideline panel members. Finally, a written summary of the available data was also created and distributed by the abstractor.

Estimation of Doses

In many published case reports of childhood poisonings, only a total dose of the drug and age of the child are given, without the child's weight. In order to compare case reports, a dose per kilogram body weight was estimated by using the child's age, sex, and the 95th percentile weight using standardized growth charts. If the dose and patient age were given but the patient's sex was not reported, the 95th percentile for boys at that age was used. Such calculated doses are shown in italics where appropriate throughout the guideline. Table 4 in the original guideline document utilizes this method of dose calculation to compare case report outcomes.

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 in 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 record of accomplishment 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 the end-users of the guideline.

Guideline Writing and Review

A guideline draft was prepared by the primary 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 primary author for response. The primary 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 primary 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.

Grade of Recommendation	Level of Evidence
A	1a
	1b
	1c

Grade of Recommendation	Level of Evidence
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 the 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 in 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 primary author. The primary author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the panel, the final revision of the guideline was prepared.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the weight of the evidence (A-D, Z) and classes of recommendations (1a-6) can be found at the end of the "Major Recommendations" field.

1. Patients with suspected self-harm or who are the victims of malicious administration of a tricyclic antidepressant (TCA) should be referred to an emergency department immediately **(Grade D)**.

2. Patients with acute TCA ingestions who are less than 6 years of age and other patients without evidence of self harm should have further evaluation including standard history taking and determination of the presence of co-ingestants (especially other psychopharmaceutical agents) and underlying exacerbating conditions, such as convulsions or cardiac arrhythmias. Ingestion of a TCA in combination with other drugs might warrant referral to an emergency department. The ingestion of a TCA by a patient with significant underlying cardiovascular or neurological disease should cause referral to an emergency department at a lower dose than for other individuals. Because of the potential severity of TCA poisoning, transportation by Emergency Medical Services, with close monitoring of clinical status and vital signs en route, should be considered **(Grade D)**.
3. Patients who are symptomatic (e.g. weak, drowsy, dizzy, tremulous, palpitations) after a TCA ingestion should be referred to an emergency department **(Grade B)**.
4. Ingestion of either of the following amounts (whichever is lower) would warrant consideration of referral to an emergency department:
    - An amount that exceeds the usual maximum single therapeutic dose or
    - An amount equal to or greater than the lowest reported toxic dose

    For all TCAs except desipramine, nortriptyline, trimipramine, and protriptyline, this dose is >5.0 mg/kg. For desipramine it is >2.5 mg/kg; for nortriptyline it is >2.5 mg/kg; for trimipramine it is >2.5 mg/kg; for protriptyline it is >1.0 mg/kg. This recommendation applies to both patients who are naïve to the specific cyclic antidepressant and to patients currently taking cyclic antidepressants who take extra doses, in which case the extra doses should be added to the daily dose taken and then compared to the threshold dose for referral to an emergency department **(Grade B/C)**.

5. Do not induce emesis **(Grade D)**.
6. The risk-to-benefit ratio of prehospital activated charcoal for gastrointestinal decontamination in TCA poisoning is unknown. Prehospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present. Do not delay transportation in order to administer activated charcoal **(Grades B/D)**.
7. For unintentional poisonings, asymptomatic patients are unlikely to develop symptoms if the interval between the ingestion and the initial call to a poison center is greater than 6 hours. These patients do not need referral to an emergency department facility **(Grade C)**.
8. Follow-up calls to determine the outcome for a TCA ingestions ideally should be made within 4 hours of the initial call to a poison center and then at appropriate intervals thereafter based on the clinical judgment of the poison center staff **(Grade D)**.
9. An electrocardiogram or rhythm strip, if available, should be checked during the prehospital assessment of a TCA overdose patient. A wide-complex arrhythmia with a QRS duration longer than 100 msec is an indicator that the patient should be immediately stabilized, given sodium bicarbonate if there is a protocol for its use, and transported to an emergency department **(Grade B)**.
10. Symptomatic patients with TCA poisoning might require prehospital interventions, such as intravenous fluids, cardiovascular agents, and

respiratory support, in accordance with standard advanced cardiac life support (ACLS) guidelines as outlined by the American Heart Association **(Grade D)**.

11. Administration of sodium bicarbonate might be beneficial for patients with severe or life-threatening TCA toxicity if there is a prehospital protocol for its use **(Grades B/D)**.
12. For TCA-associated convulsions, benzodiazepines are recommended **(Grade D)**.
13. Flumazenil is not recommended for patients with TCA poisoning **(Grade D)**.

Dosage and follow-up recommendations are summarized in Appendix 4 in the original guideline document.

Definitions:

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

CLINICAL ALGORITHM(S)

An algorithm is provided in Appendix 4 of the original guideline document for triage of tricyclic antidepressant ingestion.

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 initial management of patients with suspected ingestion of tricyclic antidepressants

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the U.S. While the toxicity of tricyclic antidepressants is not expected to vary in a clinically significant manner in other nations, the 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 the assessment of current scientific and clinical information. The panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all the circumstances involved. This guideline does not substitute for clinical judgment.

Limitations of the Published Data

Overall, the level 4 data were difficult to interpret and summarize. The case reports and case series varied widely in the extent of clinical detail presented, and the cases varied widely in the severity and clinical effects of poisoning; the timing, combination, dose, and routes of various treatments used; and in a number of other patient- or circumstance-specific factors.

Data on the amount ingested were often inaccurate or incomplete. The history is often obtained from an intoxicated patient or an emotionally stressed or elderly caregiver. Parents might underestimate or overestimate an ingested dose because of denial or anxiety. Poison center personnel often use the worst-case scenario to estimate an ingested dose in order to provide a wide margin of safety. In most case reports and case series, the history of exposure was not independently verified or confirmed by laboratory testing. Poor correlation between reported estimated doses and subsequent concentrations or toxicity has been documented for children with unintentional ingestions of other drugs. In most of the cases reviewed, the exact time of ingestion was not reported or was not known, and the time of onset of toxicity could only be estimated as occurring within a range of hours after the suspected ingestion.

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)

Woolf AD, Erdman AR, Nelson LS, Caravati EM, Cobaugh DJ, Booze LL, Wax PM, Manoguerra AS, Scharman EJ, Olson KR, Chyka PA, Christianson G, Troutman WG, American Association of Poison Control Centers. Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007;45(3):203-33. [311 references] PubMed

ADAPTATION

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

DATE RELEASED

2006 Jul 19

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

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Booze's husband is employed by AstraZeneca. Dr. Erdman is currently employed by AstraZeneca but was not during his contribution to the development of this guideline. 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 on November 30, 2006. The information was verified by the guideline developer on December 13, 2006.

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Date Modified: 10/13/2008