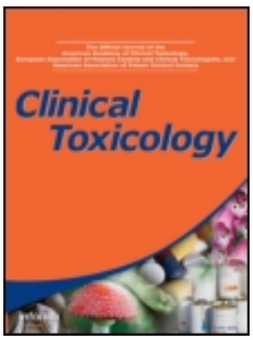

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Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management

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PRACTICE GUIDELINE

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

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A review of U.S. poison center data for 2004 showed over 12,000 exposures to tricyclic antidepressants (TCAs). A guideline that determines the conditions for emergency department referral and prehospital care could potentially optimize patient outcome, avoid unnecessary emergency department visits, reduce healthcare costs, and reduce life disruption for patients and caregivers. An evidence-based expert consensus process was used to create the guideline. Relevant articles were abstracted by a trained physician researcher. The first draft of the guideline was created by the lead author. The entire panel discussed and refined the guideline before distribution to secondary reviewers for comment. The panel then made changes based on the secondary review comments. The objective of this guideline is to assist poison center personnel in the appropriate prehospital triage and management of patients with suspected ingestions of TCAs by 1) describing the manner in which an ingestion of a TCA might be managed, 2) identifying the key decision elements in managing cases of TCA 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 TCAs alone. Co-ingestion of additional substances could require different referral and management recommendations depending on their combined toxicities. 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. Recommendations are in chronological order of likely clinical use. The grade of recommendation is in parentheses. 1) Patients with suspected self-harm or who are the victims of malicious administration of a 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 EMS, 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 mg/kg. For despiramine it is >2.5 mg/kg; for nortriptyline it is >2.5 mg/kg; for trimipramine it is >2.5 mg/kg; and for protriptyline it is >1 mg/kg. This recommendation applies to both patients who are naïve to the specific TCA 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 (Grades 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

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appropriate intervals thereafter based on the clinical judgment of the poison center staff (Grade D). 9) An ECG 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 ACLS guidelines (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).

Keywords Antidepressive agents, tricyclic/poisoning; Poison control centers/standards; Practice guidelines

Introduction

Statement of the scope of the problem and importance of the guideline

Tricyclic antidepressant (TCA) poisoning is common in the United States. In 2004, the Toxic Exposure Surveillance System (TESS) national database of poison center calls maintained by the American Association of Poison Control Centers (AAPCC) recorded 7,430 exposures to amitriptyline, 185 to desipramine, 1,288 to doxepin, 819 to imipramine, 1,152 to nortriptyline, and 26 to protriptyline, as well as 1,152 exposures to "other" or unknown cyclic antidepressants and 182 exposures to a cyclic antidepressant formulated with a benzodiazepine or phenothiazine. Within the 12,234 exposures in these categories, there were 1,351 (9%) exposures in children less than 6 years of age and 3,881 (32%) exposures described as unintentional. A total of 9,324 (76%) exposures were treated in healthcare facilities (1). The high referral rate reflects the potential toxicity of this class of pharmaceuticals.

The toxicity of TCAs was apparent relatively soon after their introduction. One case series reported two deaths in 10 adults hospitalized in 1968 for TCA poisoning (2). A review of 111 TCA deaths reported to a coroner's office over 8 years in the 1970s and early 1980s found that 71% had died in the field and another 13% were dead on arrival at a hospital (3). In a 5-year cohort study of 172,598 patients on antidepressants reported in 1995, eight of the 50 patients who committed suicide did so by antidepressant poisoning (4). Table 1 shows the deaths attributed solely to unintentional exposures to TCA (no apparent co-ingestants) culled from the TESS database for 1985–2003. In 2004, there were 85 TCA-related poisoning deaths reported in the TESS database, all of which were intentional and/or involved co-ingestants (1). Fifty-one (60%) of these intentional deaths were associated with amitriptyline.

TCA poisoning is also a cause of important morbidity. One poison center-based study reported in 1993 that, over a 2-year period, TCAs alone accounted for 25% of all overdose-induced convulsions (5). In a 1995 retrospective study of 388 consecutive patients with TCA poisoning admitted to the Fernand Widal Hospital in Paris over a 4-year period, 6.2% developed grand mal seizures, although this figure could underestimate the risk since some patients had also ingested benzodiazepines, which have anticonvulsant properties (6).

Appropriate referral to healthcare facilities is critically important as TCA ingestion can result in convulsions, coma, life-threatening arrhythmias and cardiac conduction disturbances, and death. Despite the frequency and severity of TCA poisoning, there is little consensus among poison centers on how patients should be managed in the prehospital setting.

Toxicity of different cyclic antidepressants

A prospective study of 489 patients with TCA overdoses performed in the 1970s (including 203 amitriptyline, 68 imipramine, 27 nortriptyline, 27 trimipramine, 22 clomipramine, and 21 doxepin cases), found no significant differences in clinical course between individual antidepressants (7). However, a cohort study comparing death rates per million prescriptions written in Great Britain showed TCAs such as amitriptyline and imipramine to be more toxic than other antidepressants (8). A 6-year review of annual mortality rates per million prescriptions written for antidepressants in Great Britain during 1987–92 showed TCAs generally had the highest mortality rates, with desipramine, amitriptyline, and imipramine contributing disproportionately to deaths, whereas there were no protriptyline-related deaths (9). Another British study of 3,185 fatalities due to antidepressants found doxepin to have a disproportionately higher case fatality rate (CFR) among the elderly. High mortality rates were also associated with amitriptyline, trimipramine, imipramine, and clomipramine (10). A 3-year, poison center-based review of 1,313 patients with TCA poisoning reported by Wedin et al. in 1986 (11) found that 18% of patients ingesting imipramine suffered convulsions, which was higher than other TCAs and similar to convulsion rates found with overdoses of antidepressants such as amoxapine and maprotiline. A secondary analysis of comparative CFRs of five TCAs using the TESS database for 1983–2002 found that the CFR of desipramine was 4–12-fold higher than the CFRs of amitriptyline, doxepin, imipramine, and nortriptyline (12,13). Thus, there may be some differences between individual TCA agents in terms of their potential for producing toxicity.

Pharmacology and pharmacokinetics

The neuropharmacology of TCA action is incompletely understood. Some of the therapeutic effects of TCAs on

Table 1. 1985–2003 TESS TCA deaths (single drug, unintentional)

Age/sex	TCA	Dose/serum concentration	Circumstances
13 mo/F	I	Empty bottle/unk time	Coma at home, cardiac arrest in ED, cerebral anoxia. Died 36 hr after admission.
18 mo/M	I	Whole bottle	30 mins to ED. Seizures, arrest, lavage, lorazepam, dopamine, $NaHCO_3$. Hypotension, widened QRS 5 hr later, seizure, arrhythmias, died 27.5 hr after admission.
30 yr/F	I	Empty bottle	No pulse. DOA.
10 mo/F	De	600 mg	Coma at home; To ED 90 mins after ingestion. Lavaged, ventricular fibrillation, pH 6.9, CPR, dead within 1 hr.
11 mo/M	De	Possibly 1 tablet	ED by 1 hr. Ataxic, lavage, activated charcoal, seizure, arrest.
15 mo/M	De	500 mg 2556 ng/mL	Coma, hypotension. Intubated, ventilated, dopamine, NE, died 2nd d after admission.
19 mo/F	De	Unk dose/time 1377 ng/mL	Seizure, cardiac arrest at home; pH 6.9; cerebral edema, ileus, diabetes insipidus, brain dead 4 d after admission. Multiple-dose activated charcoal, $NaHCO_3$, epinephrine, isoproterenol, atropine, Fab, mannitol, furosemide, hyperventilated.
20 mo/M	De	800 mg 1600 ng/mL	Seizure, hypotension, widened QRS. Within 2 hr of ED admission, 2 cardiac arrests and died. Phenytoin, $NaHCO_3$, pacer, physostigmine.
20 mo/F	De	Unk dose	Seizure at home, skin grey, intubated, p = 60, DOA.
2 yr/F	De	1250 mg 3900 ng/mL	Vomited at home, apnea, cardiac arrest in car, DOA.
2 yr/M	De	1250 mg 8000 ng/mL	ED by 45 min. Seizure, bradycardia, arrest. ACLS, intubation/atropine, NE, pacing. Dead at 1 hr.
3 yr/M	Do	Unk dose/time	Coma, cardiac arrest at home. DOA.
5 yr/?	Do	900 mg	Therapeutic error? Vomited; found dead at home.
84 yr/M	Do	AOC: 200 mg	Coma, respiratory depression.
17 mo/M	A	Unk dose/time	Seizure, pneumothorax. $NaHCO_3$, intubated, ventilation, dopamine, NE, diazepam. Died on 12th d.
3 yr/M	A	100–125 mg	Cyanosis, coma, DOA
5 yr/M	A	Unk dose/time A 1150 ng/mL N 790 ng/mL	DOA. Necrotizing pneumonia & pulmonary edema at autopsy.
5 yr/M	N	Unk dose 851 ng/mL	Coma, hyperthermic, hypotensive, aspiration pneumonia, arrhythmias. Intubated, ventilated, lidocaine, NE, bretylium, $NaHCO_3$, dopamine, antibiotics. Multisystem failure over 5 d.

ED: emergency department; Fab: Digoxin Fab anti-digoxin antibodies; CPR: cardiopulmonary resuscitation; AOC: acute on chronic; ACLS: advanced cardiac life support; DOA: dead on arrival at emergency department; $NaHCO_3$: sodium bicarbonate; NE: norepinephrine; Unk: unknown; TCA: I = imipramine, De = desipramine, A = amitriptyline, Do = doxepin, N = nortriptyline.

clinical depression have been attributed to their ability to deplete norepinephrine (NE) from neuronal presynaptic vesicles, selectively inhibit NE transport, and block NE reuptake. There are variable inhibitory effects on serotonin uptake-inactivation as well. TCAs have both central and peripheral anticholinergic properties. Delayed gastric emptying time and slowed intestinal peristalsis associated with such effects could account in part for the variable absorption rates and delayed clinical toxicity seen in TCA poisoning. TCAs also affect cardiac conduction by blocking fast inward Na^+ channels on myocardial cells, analogous to type Ia antiarrhythmic drugs. Such actions can lead to arrhythmias and cardiac conduction disturbances. Blockade of postsynaptic peripheral α-adrenergic receptors decreases preload and vascular resistance and contributes to the hypotension associated with TCA use (14).

TCAs have narrow dosage ranges for therapeutic efficacy; higher doses are anticipated to produce adverse effects. A trial in 173 children and adolescents found that single doses of 3.75 mg/kg of desipramine produced serum concentrations of 45 ng/mL and clearance rates of 0.74 L/kg/hour with no significant age- or gender-related variation in pharmacokinetics (15). The prolonged clinical effects of TCAs could be related to slow absorption, their large volumes of distribution (10–50 L/kg), and the enterohepatic recirculation of both parent compound and metabolites. In overdose, the half-life for amitriptyline elimination (without decontamination or enhanced elimination therapies) averages almost 37 hours and is commonly greater than 60 hours (16).

Therapeutic dosages and uses

Table 2 presents the recommended therapeutic dosage ranges for the medications covered in this guideline. TCAs are frequently prescribed for depression, panic attacks, severe anxiety, phobic disorders, obsessive-compulsive disorders, eating

Table 2. Current formulations and dosing recommendations for tricyclic antidepressants (309–311)[*†]

Amitriptyline HCl tablets (Elavil[‡], Endep): 10, 25, 50, 75, 100, 150 mg
Adults: 40–100 mg initially and daily maintenance (max 150–300 mg daily)
Adolescents & elderly: 10 mg TID and 20 mg q HS (maximum: 200 mg daily)

Clomipramine HCl capsules (Anafranil): 25, 50, 75 mg
Adults: 25 mg initially to 100 mg maintenance (max 300 mg daily)
Children (10–18 years old): 25 mg initially to 100 mg (or 3mg/kg) maintenance (max 200 mg daily)

Desipramine HCl tablets (Norpramin): 10, 25, 50, 75, 100, 150 mg
Adults: 100–200 mg (max 300 mg daily in hospitalized patients)
Adolescents & elderly: 25–100 mg (max 150 mg daily)
Child (6–12 years old): 1–3 mg/kg/day (max 5 mg/kg/day)

Doxepin HCl capsules (Sinequan): 10, 25, 50, 75, 100, 150 mg; oral concentrate 10 mg (base)/ mL
Adults: 25–75 mg (max 300 mg daily – max single dose: 150 mg)
Child: 1–3 mg/kg/day

Doxepin cream (Prudoxin, Zonalon): 5%; each g = 50 mg doxepin HCl
As directed QID.

Imipramine HCl tablets (Norfranil, Tipramine, Impril, Janimine, Novopramine, Tofranil): 10, 25, 50 mg
Impiramine pamoate capsules (Tofranil-PM): 75, 100, 125, 150 mg
Adults: 75–100 mg daily (max 200 mg daily; 300 mg daily for hospitalized patients only)
Adolescents & elderly: 30–40 mg daily (max 100 mg daily)
Children: >5 yr of age 1.5–2.5 mg/kg/day (max 5 mg/kg/d)
Child (enuresis, in 6–12 years old): 25–50 mg at bedtime
Child (enuresis, in ≥12 year olds) 25–75 mg (max 2.5 mg/kg)

Nortriptyline HCl capsules (Aventyl, Pamelor): 10, 25, 50, 75 mg; oral concentrate 10 mg/5 mL
Adults: 25 mg TID or QID (max 150 mg daily)
Adolescents & elderly: 30–50 mg daily (max 50 mg daily)
Children 6–12 years old: 1–3 mg/kg/day or 10–20 mg/day

Protriptyline HCl tablets (Vivactil): 5, 10 mg
Adults: 15–40 mg daily in divided doses (max 60 mg daily)
Adolescents & elderly: 15 mg daily initially (max 20 mg daily)

Trimipramine maleate capsules (Surmontil): 25, 50, 100 mg
Adults: 75–100 mg in divided doses (max 150 mg outpatients; 200 mg hospitalized patients)
Adolescents & elderly: 50 mg daily (max 100 mg daily)

Tricyclic Antidepressants in Combination
Perphenazine & amitriptyline HCl tablets (Etrafon, Triavil): 2/10, 2/25, 4/10, 4/25, 4 mg/50 mg
Amitriptyline dosing same as above

Chlordiazepoxide & amitriptyline HCl tablets (Limbitrol): 5/12.5, 10 mg/ 25 mg
Amitriptyline dosing same as above

*Manufacturers specify to use their lower maximum doses in outpatient, unmonitored settings.
†Manufacturers do not recommend most tricyclic antidepressants for use in children.
‡Elavil is no longer marketed in the U.S.

disorders, and attention deficit hyperactivity disorders (14,17). They have also been used for a variety of other conditions including pain syndromes, insomnia, cataplexy, migraines, fibromyalgia, chronic fatigue, irritable bowel syndrome, and peptic ulcer disease (14,18). Doxepin cream is used for relief of localized pain and for itching.

Clinical toxicity

Typical side effects seen in patients given therapeutic doses of TCAs include anticholinergic symptoms, such as tachycardia, mydriasis, dry mouth, warm flushed dry skin, delayed gastric emptying, slowed intestinal peristalsis or even ileus, urinary retention, and confusion or agitation. Headache, fatigue, anxiety, increased intraocular pressure, blurred vision, drowsiness, weakness, dizziness, and restlessness are also common, as are gastrointestinal complaints including constipation, anorexia, nausea, and epigastric distress (19). Other adverse effects include ophthalmoplegia or paralysis of gaze (20,21) and acute pancreatitis (22).

The cardinal features of severe poisoning include life-threatening cardiac arrhythmias and conduction disturbances,

abrupt changes in level of consciousness, coma, convulsions, hypotension, and sudden death. Pulmonary complications (e.g., respiratory depression, sudden apnea, aspiration pneumonia, adult-type respiratory distress syndrome, and pulmonary edema) can be life threatening. Other signs of TCA poisoning include palpitations, tachycardia, hypertension, ileus, tremors, myoclonus, confusion, delirium, and lethargy.

Definition of terms used in this guideline

Toxicity from TCAs can 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 in a patient already on the drug, unintentional ingestion of someone else's therapeutic dose in a patient not taking a TCA, unintentional ingestion by a child, or intentional ingestion.

This guideline focuses on the ingestion of more than a single therapeutic dose. It is known that even therapeutic doses of TCAs can sometimes cause adverse effects in both adults and children—some idiosyncratic and some dose-dependent. However, the focus of this guideline is on the effects of TCAs in overdose. Articles that were reviewed and found to report adverse effects related to usual therapeutic doses were included if they provided useful information on the dose-response relationship.

For the purpose of this guideline, age groups are defined as 1) children less than 6 years of age and 2) older children and adults. The older age group is much more likely to attempt self-harm and to conceal the ingestion. Acute exposures are defined as those occurring over a period of no more than 8 hours, and chronic exposures are those that occur over a period of more than 8 hours. The terms "out-of-hospital" or "prehospital" are defined as the period before a patient reaches a healthcare facility.

Intended users of this guideline

The intended users of this guideline are personnel in U.S. poison centers. It 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.

Exclusions

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, dibenzipine, melipramine, prothiaden (dosulepin), and other antidepressants not currently available in the U.S. are not included in this guideline.

This guideline applies to unintentional ingestions or ingestions resulting from medication errors. Poisonings resulting from intentional abuse or self-harm will all require referral to an emergency department for evaluation. The likelihood of self-harm is greatest in adolescent and adult patients, who might also seek to conceal an overdosed. TCAs have been implicated in cases of Munchausen syndrome by proxy when parents purposefully overdose their children chronically to garner attention from healthcare providers (23,24). Likewise, TCAs have also been administered with homicidal intent or in instances of child abuse (25,26). If there is suspicion concerning the circumstances of poisoning, referral to an emergency department is of paramount importance.

Objective of the guideline

The objective of this guideline is to assist poison center personnel in the appropriate prehospital triage and management of patients with suspected ingestions of tricyclic antidepressants by 1) describing the manner in which an ingestion of a tricyclic antidepressant might be managed, 2) identifying the key decision elements in managing cases of tricyclic antidepressant 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 tricyclic antidepressants alone. Co-ingestion of additional substances could require different referral and management recommendations depending on their combined toxicities.

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.

Methodology

The methodology used for the preparation of this guideline was developed after reviewing the key elements of practice guidelines (27,28). 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 record of accomplishment 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 the end-users of the guideline.

Search strategy

The National Library of Medicine's MEDLINE database was searched (1966 to September 2003) using antidepressive agents, tricyclic as a 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 management in Poisindex (19) 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 six current major pharmacology and toxicology textbooks (14,29–33) 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 1995–2004 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) and forensic analyses without exposure details.

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 (Appendix 2). 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 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 (34). 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 utilizes this method of dose calculation to compare case report outcomes.

Guideline writing and review

A guideline draft was prepared by the primary 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 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. 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 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.

Review of the Evidence

Current poison control center practices

Because the toxic doses overlap with the upper therapeutic range for many of these drugs, some poison control centers recommend hospital evaluation after any potentially toxic TCA exposure. One survey of 44 poison centers (30 respondents or 68%) in 1999 reported that 26 of 30 poison centers (87%) sent all TCA-poisoned children to healthcare facilities regardless of dose (the other four poison centers varied in their thresholds: more than 1.5–5 mg/kg) (35). McFee et al. (36) reported a second survey of 30 poison centers (22 replies, a 73% return rate) the following year. Of 14 poison centers setting a threshold dose, six referred all children ingesting more than 5 mg/kg.

To gather additional evidence for this guideline, a request was sent out in 2004 to all U.S. poison centers for their current TCA poisoning triage guidelines. Table 3 presents a comparison of current practice of the nine poison centers that provided guidelines (seven other centers indicated that they did not have guidelines for TCA management). The range of doses for hospital referral in acute poisoning was from 3 mg/kg or "one pill" to as much as the TCA therapeutic dose (5 mg/kg). These results give evidence of the need for consensus building among poison centers nationally for uniformity in the approach to the triage of prehospital TCA exposures.

Review of textbooks

Several textbooks noted that TCA ingestions greater than 1000 mg in adults are associated with life-threatening toxicity

Table 3. Comparison of poison center guidance: tricyclic antidepressants, May, 2004

Poison center	A	B	C	D	E	F	G	H	I
Stay-home dose (child)	≤5 mg/kg	<5 mg/kg	—	one pill	<3 mg/kg	<5 mg/kg	—	Rx dose (≤6 yr), double dose (7–64 yr)	<3.5 mg/kg
Protriptyline						<1 mg/kg			
Follow-up calls	1–2, 6 hr	1–2, 4–6 hr, prn	—	—	2, 6 hr	—	—	2, 4, 6 hr	2 hr
AC	Yes	Yes	Yes	Yes, remove pill fragments	Yes	Yes	Yes	Yes	Yes
Multi-dose AC	—	No	No	Yes	Yes	—	No	Yes	—
Lavage	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ipecac	—	No	—	No	—	Not preferred	No	—	No
$NaHCO_3$ bolus	—	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
$NaHCO_3$ drip	—	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Target blood pH			7.45–7.50	7.45–7.55	7.45–7.55	7.45–7.55	7.45–7.50	7.45–7.55	<7.55
Symptoms monitored at home	Minor drowsiness	No	—	No	Minor drowsiness	—	—	Minor drowsiness, urinary retention	No

Legend: pm = as needed, AC = activated charcoal, $NaHCO_3$ = sodium bicarbonate, Rx = therapeutic.

(31–33). Some also defined a dose of 10 mg/kg or more as causing significant toxicity in children (19,29–32). None made any distinctions between individual TCA drugs in terms of potentially toxic doses. Several texts specified 6 hours after the ingestion as the period during which the onset of symptoms is likely (19,30,31,33). Some recommended 6 hours as the observation period for symptoms (assuming the patient had received oral decontamination) before a patient with TCA poisoning could be medically cleared (32,33).

Toxic dose considerations

A precise toxic threshold dose was difficult to determine from the literature for several reasons: 1) a paucity of good quality studies (no articles specifically investigated a toxic dose threshold, and only a small number of articles contained dose-effect information), 2) questions about the accuracy of the dose estimate, because the TCA was not prospectively administered and dose information relied on historical data from a witness or parent, 3) presence of coingestants (e.g., barbiturates, antipsychotics, ethanol) that could alter the clinical presentation, 4) interindividual differences in weight or TCA pharmacokinetics, and 5) a number of articles involved many patients (some of whom remaining asymptomatic) in which doses and/or effects were only reported as ranges, percentages, or means. The task was made more difficult by the fact that therapeutic doses are associated with adverse effects (e.g., sedation, heart rate and ECG interval changes). Despite these limitations, some dose-toxicity information could be gleaned from the cumulative evidence.

Minimum acute toxic dose in children less than 6 years of age

In 1967, Steel et al. (37) published a level 4 review of 31 cases of childhood amitriptyline and imipramine poisoning and cited a report of a TCA dose at 8 mg/kg as a threshold associated with severe toxicity. The lowest dose associated with a fatality in that series was 32 mg/kg, whereas one child survived despite ingesting a dose estimated at 112 mg/kg. A 1974 level 4 report of 60 children hospitalized for a one-time TCA poisoning estimated the minimum lethal dose of amitriptyline or imipramine to be 30 mg/kg, although the authors included the case of a 2½-year-old child who died within 4 hours of ingesting 15 mg/kg. While the authors listed 15 mg/kg as the dose associated with severe symptoms in their case series, they stated "…children who ingest tricyclics in whatever dosage should always be admitted…" (38).

Additionally, there was a level 2b article (39), a level 3b investigation (40), and a number of level 4 or 6 case series (41–48) in which the exact TCA ingested was not reported but in which some dose-effect information was available. The lowest dose of an unidentified TCA associated with any toxicity (described as "minor"—probably drowsiness) in a child was an ingestion of 0.5 mg/kg (47); the lowest specified dose associated with severe toxicity was up to three times the daily dose (43); and the lowest quantified dose associated with severe toxicity was 15–25 mg/kg (44). A level 6 abstract of a retrospective case series of 48 children less than 6 years of age with acute TCA poisoning found that only three of 43 children at TCA doses of 5 mg/kg or less developed any toxicity at all (described as "minimal") and that only one of the remaining five children (doses 5–9.4 mg/kg) became "sleepy" (45). Two level 4 reports (both retrospective and with few cases) investigating a toxic threshold for unintentional childhood TCA ingestion found that, while children ingesting doses of less than 5 mg/kg sometimes developed mild toxicity such as drowsiness, none developed severe poisoning (46,47).

From more than 60 published case reports of pediatric TCA poisoning reviewed (see Table 4), symptoms were reported at doses as low as 3 mg/kg. The lowest amitriptyline ingestion associated with mild toxicity was 50 mg and the lowest dose associated with death was 15 mg/kg (38). The lowest dose of desipramine associated with severe toxicity was 100 mg [*6 mg/kg*] in a 3-year-old (49). The lowest dose of imipramine associated with coma was up to 75 mg [*3 mg/kg*] by a 5-year-old, and the lowest dose associated with convulsions was an ingestion of up to 100 mg [*7.5 mg/kg*] by a 15-month-old (50). A single case involved the ingestion of 325 mg [*16 mg/kg*] nortriptyline by a 4-year-old, which resulted in severe toxicity (48).

Minimum acute toxic dose in patients 6 years of age and older

Life-threatening symptoms in adults are often seen with TCA doses in excess of 1000 mg. However, cardiac arrest has been noted with imipramine doses as low as 200 mg (51). A 22-year-old woman suffered a myocardial infarction 26 hours after ingesting 300 mg amitriptyline and 80 mg diazepam. However, in that case report there was no laboratory verification of the exposure and there was no blood or urine screening to rule out other substance abuse that might have contributed to a myocardial infarction (52). Bramble et al. (53) studied 27 acute TCA-poisoned patients prospectively (level 2b) and found that imipramine doses of 1000 mg were associated with life-threatening symptoms or death in two patients, while a patient who ingested 600 mg clomipramine suffered only mild toxicity. Three patients in that series who ingested 500–750 mg amitriptyline suffered moderate to severe symptoms. Of four patients ingesting 500–1200 mg trimipramine, the lowest dose associated with moderate toxicity was 1000 mg. There were several articles in which the exact TCA ingested was not reported but in which some dose-effect information was available. There was a single level 2b article (39), two level 3b investigations (40,51), and

Table 4. One-time overdoses of tricyclic antidepressants in children less than 6 years of age

Drug	Dose* (mg/kg)	Age sex	Onset of symptoms	Duration of toxicity	Arrhythmia	Cardiac arrest	Coma	Hypotension	Pneumonia	Pulmonary edema	Respiratory arrest	Respiratory depression	Seizure	Fatal	Ref.
A	81	15 mo F	45 min	–	X			X			X		X	Yes	228
A‡	*68*	24 mo F	–	–									X	No	42
A	36	23 mo M	–	–	X	X	X	X			X	X	X	No	197
A‡	31	24 mo F	<60 min	–			X							No	229
A‡	*19*	17 mo F	–	–			X							No	230
A	4	48 mo M	3.5 hr	24 hr										N	231
A	–	42 mo F	<180 min	24 hr	X									No	232
A	–	36 mo M	240 min	–	X		X	X						No	151
A SR§	–	60 mo M	–	–										No	233
N	*16*	48 mo	–	–										No	48
N	–	30 mo M	<120 min	–	X		X	X					X	No	232
I	*213*	24 mo M	–	–		X	X				X			Yes	163
I	*188*	30 mo M	60 min	Several d	X		X	X					X	No	173
I	*155*	30 mo M	10 min	–		X	X				X		X	Yes	234
I	*116*	35 mo M	30 min	2–3 d	X	X	X	X			X		X	No	235
I	100	20 mo M	40 min	–	X		X	X					X	No	236
I	*90*	19 mo M	<45 min	48 hr	X			X					X	No	237
I	*86*	36 mo M	–	–	X	X	X	X			X			Yes	238
I	70	? M	105 min	–	X		X	X					X	No	42
I	68	30 mo M	<14 hr	–	X		X	X					X	No	236
I	*62*	30 mo M	3.5 hr	Several d	X		X	X			X		X	No	239
I	*61*	48 mo F	–	–										No	240
I	*57*	24 mo F	30 min	–	X		X	X			X		X	Yes	241
I	60	30 mo F	–	5 d	X		X	X					X	No	232
I	*47*	36 mo F	–	2 d	X		X	X					X	No	242
I	*47*	30 mo	–	–										Yes	243
I	*44*	18 mo F	–	–	X		X				X			Yes	244
I	*40*	23 mo M	<90 min	2 d	X		X	X			X		X	No	245
I	36	44 mo M	–	2–3 d	X		X			X		X	X	No	246
I	50	20 mo M	<180 min	–	X									No	232
I	*34*	22 mo M	<120 min	24 hr	X			X					X	No	247
I	32	48 mo M	240 min	–		X	X						X	Yes	150
I	*31*	30 mo M	30 min	Several d	X	X	X	X					X	No	248
I	*31*	30 mo M	15 min	–	X	X	X	X			X		X	Yes	249
I	30	18 mo F	75 min	–	X		X	X					X	No	44
I	*26*	36 mo F	<60 min	4 d	X		X		X			X	X	No	221
I	*26*	20 mo	–	–	X		X						X	No	250
I	*25*	30 mo M	120 min	>13 hr			X							No	251
I	*25*	18 mo M	90 min	–	X		X	X					X	Yes	50
I	*25*	14 mo F	–	–	X		X	X	X		X		X	Yes	196
I	25	11 mo M	30 min	–	X	X	X	X					X	Yes	198
I	23	26 mo F	30 min	–	X		X	X	X		X		X	No	252
I	*23*	18 mo F	90 min	7 d	X		X	X				X	X	No	253
I	*21*	21 mo F	–	–									X	No	254
I	*20*	15 mo F	–	–	X		X						X	Yes	62
I	15	30 mo	240 min	–	X	X	X				X	X	X		38
I	*12*	36 mo F	–	–		X							X	No	42
I	*8*	30 mo	–	–	X								X	No	254
I	*7.5*	15 mo M	120 min	–	X			X					X	No	50
I	*5*	19 mo M	75 min	24 hr			X							No	50

(Continued)

Table 4. *(Continued)*

Drug	Dose* (mg/kg)	Age sex	Onset of symptoms	Duration of toxicity	Arrhythmia	Cardiac arrest	Coma	Hypotension	Pneumonia	Pulmonary edema	Respiratory arrest	Respiratory depression	Seizure	Fatal	Ref.
I†	*3*	60 mo M	<60 min	48 hr			X							No	50
I	–	24 mo M	6 hr	Several d			X						X	No	50
I	–	24 mo F	180 min	12 hr	X		X						X	No	255
I	–	16 mo F	?	–			X							Yes	256
I	–	15 mo M	–	–	X		X						X	No	205
De	*171*	24 mo F	<60 min	–	X		X	X	X				X	Yes	257
De	65	19 mo M	90 min	28 hr	X		X				X	X	X	No	214
De	30	19 mo F	–	–	X		X						X	Yes	44
De	*6*	15 mo	–	–											49

*Italics indicate estimated dose from the child's weight at 95th percentile for age.
†Co-ingestant thioridazine.
A = amitriptyline.
A-SR = amitriptyline, sustained release.
‡Co-ingestant perphenazine.
N = nortriptyline.
De = desipramine.
§Co-ingestant orphenadrine.
I = imipramine.

eight level 4 case series (41–44,48,54–56). Among all of these retrospective investigations, the lowest dose of an unidentified type of TCA associated with mild toxicity was 200 mg (48), the lowest semi-quantified dose associated with severe toxicity was up to three times the daily dose (43), and the lowest quantified dose associated with severe toxicity was 15–25 mg/kg (44).

Amitriptyline

There were two prospective, randomized, controlled trials (level 1b) in which a dose of 12.5 mg amitriptyline, given to healthy adults, was associated with sedation (57,58). In a level 1b, double-blind study of 12 adults, "auditory vigilance" was impaired within 1½ hours of administration of 6.25 mg amitriptyline and lasted 5 hours (57). There were a number of articles in which the recognition of the amitriptyline ingestion was retrospective, so there was uncertainty about the actual amount ingested. Among these were five level 2b articles (16,53,59–61), a single level 3b article (62), and five level 4 articles (6,48,63–65). Also, there were over 50 level 4 or 6 articles in which detailed information was presented concerning 65 cases (see Table 5). Among these, the lowest dose of amitriptyline associated with mild toxicity was 50 mg (38) and the lowest dose associated with severe toxicity was 300 mg (52).

Clomipramine

There was a single level 2b study (53) and four level 4 case series or case reports (6,22,48,66) that provided information on dose-effect relationships for clomipramine. The lowest dose associated with mild toxicity was 600 mg (53), and the lowest associated with severe toxicity was 750–1500 mg (22).

Desipramine

There were 10 level 4 articles with individual case information on dose-effect relationships for desipramine (54,67–75). The lowest dose of desipramine associated with severe toxicity was 1000–1200 mg (70).

Doxepin

Some subjects in a self-controlled, level 2b trial of eight adult volunteers taking doxepin 50 mg after an overnight fast experienced pronounced sedation between 30 minutes and 3 hours after ingestion (76). There were two level 4 retrospective case series containing dose-effect information for doxepin (48,65), and there were eight individual cases reported in seven level 4 articles (71,77–82). Among these, the lowest doxepin dose associated with toxicity was in a 23-year-old man who died after taking nine tablets (tablet strength not reported; total dose could have been as low as 1.3 mg/kg [90 mg total dose] or as high as 19 mg/kg [1350 mg total dose]) (82). A 24-year-old woman developed severe toxicity (AV block, hypotension and respiratory failure) with eventual recovery after ingesting 425 mg doxepin but she had concomitantly taken 2500 mg amitriptyline and 1125 mg desipramine (71). Death was reported after an ingestion of up to 1500 mg of doxepin (80). Vohra et al. (65) reported a 42-year-old woman who became unconscious after ingesting 750 mg doxepin and a 19-year-old who experienced only drowsiness after ingesting 575 mg doxepin; both survived.

Table 5. One-time overdoses of tricyclic antidepressants in patients 6 years of age and older

Drug	Dose (mg)	Age (yr) sex	Onset (hr)	Duration	Survived	Ref.
A	10,000	32 F	–	–	Yes	251
A	9000	46 F	1	Several d	Yes	258
A	8000	45 M	–	–	Yes	219
A*	6300	30 F	–	–	No	259
A*	6000	38 M	–	7 d	Yes	260
A†	6000	35 F	–	–	Yes	204
A	6000	29 M	1	–	Yes	261
A	5000	30 F	–	5 d	Yes	260
A	3750	23 M	2.5	–	Yes	262
A*	3750	25 F	3	3 d	Yes	263
A	3000	36 M	–	2 d	Yes	264
A*	2750	31 F	–	–	Yes	265
A	2500	42 F	2	36 hr	Yes	266
A	2500	70 F	3	–	Yes	267
A	2200	57 M	–	16 mo	Yes	268
A*	2000	26 F	–	–	No	269
A†	2000	39 F	–	4 d	Yes	202
A	2000	47 M	–	2 d	Yes	270
A	1875	23 F	–	–	Yes	86
A	1750	19 F	–	–	Yes	271
A	1500	30 F	–	–	Yes	272
A*	1500	38 M	–	–	Yes	86
A*	1300	41 F	1	Several d	Yes	273
A*	1250	– F	–	–	Yes	265
A†	1250	25 M	–	–	No	274
A*	1250	56 M	–	–	No	159
A	1200	42 M	–	–	Yes	275
A	1050	14 F	–	Several d	Yes	276
A*	1050	17 M	–	–	Yes	93
A	1000	24 M	2	24 hr	Yes	277
A*	1000	35 F	–	–	Yes	117
A	1000	61 M	9	–	Yes	278
A†	1000	65 M	2	Several d	Yes	279
A	1000	67 M	4.5	48 hr	Yes	280
A	950	70 F	4.5	–	No	280
A	800	53 F	–	–	Yes	281
A*	850	67 F	1	3.5 hr	No	3
A*	750	14 M	–	–	Yes	230
A†	750	44 M	16	Several d	Yes	155
A	750	45 F	–	13 d	No	259
A	525	8 M	–	–	Yes	229
A	500	45 F	3		Yes	262
A	350	33 F	–	–	Yes	117
A*	300	22 F	–	36 hr	Yes	52
A*	200	46 F	1	–	Yes	196
A	150	52 F	–	–	Yes	21
A*	–	13 M	–	–	Yes	230
A*	–	18 M	–	–	Yes	149
A	–	22 F	–	–	Yes	151
A*	–	22 F	–	–	Yes	151
A	–	24 F	–	–	Yes	265
A*	–	24 F	2	–	Yes	152
A	–	25 F	–	–	Yes	282
A*	–	27 F	–	–	No	182
A	–	28 F	–	4 d	Yes	260
A	–	28 F	2	–	Yes	93

(Continued)

Table 5. *(Continued)*

Drug	Dose (mg)	Age (yr) sex	Onset (hr)	Duration	Survived	Ref.
A	–	31 F	–	3 d	Yes	152
A	–	33 M	–	–	No	283
A*	–	34 F	–	7 d	No	284
A*	–	35 F	–	–	Yes	149
A*	–	38 F	1	–	No	219
A*	–	39 F	–	Several d	Yes	190
A*	–	39 F	–	Several d	Yes	285
A	–	44 F	–	–	Yes	286
A	–	44 M	12	–	Yes	287
A*†	–	44 M	–	50 hr	No	92
A*	–	46 F	2	56 hr	No	154
A	–	47 F	–	–	No	269
A*	–	55 F	–	8 d	Yes	288
A*	–	56 F	0.25	–	Yes	222
A	–	16 F	–	3 d	Yes	226
A	–	63 M	–	3 d	Yes	213
A/I	1000	9 F	–	2 wk	Yes	289
A/I*	–	47 F	2	–	Yes	222
A/I*	–	50 F	6	4 hr	Yes	290
A/N*	–	34 F	3	40 hr	No	2
C*	15,000	27 M	5	>4 d	Yes	66
C	750	48 F	6	2 weeks	Yes	22
De	9000	15 F	–	–	No	73
De	2700	14 F	–	–	Yes	75
De	2500	40 F	–	–	Yes	54
De	2000	24 F	4	–	Yes	69
De	1800	22M	7	19 hr	Yes	72
De*	1500	38 F	2	–	No	68
De	1500	19 F	4	–	Yes	67
De*	1200	18 F	12	–	Yes	70
De	1150	58 F	1.5	Several hr	Yes	74
De	–	19 F	–	–	Yes	189
De	–	31M	–	–	Yes	218
De*	–	27 F	–	–	No	2
Do*	3000	55 M	–	–	Yes	77
Do*	2500	24 M	1	–	No	78
Do	1500	35 F	3	–	No	80
Do	1500	54 F	1	24 hr	Yes	81
Do*	600	34 M	4	–	Yes	79
Do	–	18 F	2	–	No	152
Do	–	23 M	1	13 hr	No	82
Do*	–	49 F	–		Yes	291
Do*	–	53 F	–	–	Yes	117
I*	10,000	34 F	–	–	No	54
I*	5375	21 F	3.5	Several d	Yes	292
I	5350	23 F	1.5	–	Yes	171
I	4700	41M	–	Several d	Yes	293
I	4500	25 F	–	–	Yes	188
I	2500	30 F	–	–	Yes	294
I	2500	14 F	2	–	Yes	211
I	2250	19 F	0.66	Several d	Yes	295
I	1875	38 F	–	–	No	296
I*	1500	14 F	–	–	Yes	199
I	1500	29 F	8	3 d	Yes	297
I	1250	19 F	0.75	–	Yes	209

(Continued)

Table 5. *(Continued)*

Drug	Dose (mg)	Age (yr) sex	Onset (hr)	Duration	Survived	Ref.
I	1250	24 F	–	–	Yes	136
I*	1150	38 F	2	–	Yes	298
I†	1000	6 M	4	–	Yes	299
I†	1000	8.5 M	–	–	No	300
I*	1000	47 F	–	–	No	159
I†	800	32 M	–	–	Yes	133
I	750	7 M	4	–	Yes	300
I	750	36 F	–	–	No	301
I†	625	28 F	2	–	No	302
I	475	7 F	–	–	Yes	303
I	–	10 M	–	–	No	210
I	–	18 M	–	–	No	54
I	–	24 F	–	–	No	304
I	–	25 F	–	–	Yes	305
I	–	27 F	1.5	–	Yes	306
I	–	27 F	–	–	Yes	212
I	–	28 M	1	–	No	209
I	–	29 F	–	–	Yes	54
I	–	34 F	10	–	Yes	307
I	–	36 F	–	–	No	137
I	–	37 F	–	–	No	137
I*	–	40 M	–	–	Yes	308
I	–	49 F	–	5 d	No	153
I	–	54 F	–	–	Yes	200
N	8000	29 F	0.25	–	Yes	90
N	5000	52 F	–	–	Yes	89
N	2350	69 F	2	10 hr	No	82
N	2000	30 F	–	17 hr	No	91
N*†	1250	21 F	–	–	No	92
N	1250	59 M	–	–	Yes	86
N	950	19 F	0.75	–	Yes	87
N*	600	25 F	4	24 hr	Yes	85
N	–	16 F	–	–	No	88
N	–	34 F	–	–	No	151
P	–	28 M	–	–	No	201
T*	3500	21 F	–	–	Yes	93
T*	–	59 F	–	–	Yes	93
Unk*	–	39 F	–	–	Yes	207
Unk	–	45 M	–	–	Yes	208

*Co-ingestant confirmed.
†Acute-on-chronic poisoning.
A = amitriptyline.
C = clomipramine.
De = desipramine.
Do = doxepin.
I = imipramine.
N = nortriptyline.
P = protriptyline.
T = trimipramine.

Imipramine

There was one level 1b, prospective, randomized trial in which a single 12.5 mg dose of imipramine given to healthy adults resulted in sedation and dry mouth (83). There were a number of articles in which the recognition of imipramine ingestion was retrospective. There was a single level 2b article (53), a single level 3b article (51), two level 4 case series (38,84), and 30 cases in 28 level 4 or 6 case reports, case series, or their abstracts. The lowest dose of imipramine associated with toxicity was 100 mg (38); the lowest fatal dose was 200 mg (51).

Nortriptyline

There was a single level 1b, prospective, randomized trial in which single nortriptyline doses of 12.5 mg given to healthy adults were associated with sedation, impairment in reaction, and poor performance of complex tasks (57). There were several articles in which the recognition of nortriptyline ingestion was retrospective. There was a single level 2b article (85), two level 4 case series (63,84), and nine individually reported cases (82,85–92). Among these, the lowest dose of nortriptyline associated with severe toxicity was 600 mg (85).

Trimipramine

There was a single level 2b study (53), a single level 4 case series (6), and a single case report (93) of trimipramine ingestion. Among these, the lowest dose of trimipramine associated with moderate toxicity was 1000 mg (53) and the lowest dose resulting in severe toxicity was 1200 mg (6).

Protriptyline

There are few studies of protriptyline toxicity. In one level 1b adult study, some functions (tapping rate, arithmetic function, and reaction time) were perturbed with 25 mg doses of amitriptyline and nortriptyline, whereas a therapeutic dose of protriptyline (10 mg) produced no functional disturbances. Both nortriptyline and protriptyline (secondary amines) were associated with much less sedation than amitriptyline (tertiary amine) at such doses (57).

Chronic therapeutic TCA dosing in children less than 6 years of age

Therapeutic doses of TCAs produce severe symptoms of toxicity in some children. One child in a prospective trial (level 1b) of imipramine developed listlessness and constipation on 50 mg/day (94). In a level 3b study, children treated with desipramine (mean dosage 3 mg/kg/day) had increases in the PR intervals on their ECGs (95). A 3-year-old boy with autism was treated with amphetamines and imipramine (25 mg three times daily, increased to 50 mg three times daily after several weeks). One week after the upward dose revision, he developed tremors, convulsions, and then hypotonia, which abated after the medications were discontinued (96). Another 3-year-old with autism also developed convulsions 2 days after reinitiating imipramine treatment at 75 mg daily. He had previously been on the drug at 125 mg daily for an unspecified period but had had a 15-day hiatus. He continued to have convulsions throughout his early life, despite discontinuation of the imipramine and initiation of anticonvulsant treatment (97).

Chronic therapeutic TCA dosing in patients 6 years of age and older

Therapeutic dosages of TCAs have adverse effects on consciousness, cognitive function, and cardiovascular status. There was a single level 1b prospective trial in which mean dosages of 3 mg/kg/day of either clomipramine or desipramine were associated with mean increases in heart rate and prolonged PR, QRS, and QTc intervals (98). In a prospective, unblinded trial of imipramine's effects on depression in 44 adults, patients receiving 3.5 mg/kg/day in divided doses (mean 245 mg daily in men and 218 mg daily in women) experienced orthostatic hypotension, dizziness, ataxia, and falls (99). A meta-analysis by Wilens et al. (100) (level 1a) aggregated 24 studies involving 730 children and adolescents given imipramine, desipramine, or amitriptyline at doses of 0.7–5 mg/kg (mean 3.7 mg/kg) or nortriptyline at doses of 0.6–2 mg/kg and found only minor effects on ECG conduction parameters, heart rate, and blood pressure. However, therapeutic doses of TCA taken chronically have been associated with cardiovascular complications and sudden death in older children and adolescents (100–106).

Amitriptyline

Two level 1b trials (107,108) and several level 2b prospective trials (65,109–112) examined amitriptyline given prospectively. Among them, the lowest dosage associated with toxicity was 100–200 mg/day, resulting in increased heart rate and the prolongation of ECG intervals (110). There were also eight reports of chronic amitriptyline toxicity in five level 4 articles (110,114–117). Among these, the lowest dosage associated with toxicity was 50 mg/day, resulting in pedal edema and adynamic ileus (110). A 73-year-old woman was erroneously prescribed 100 mg tablets instead of 10 mg of amitriptyline (200 mg daily instead of 20 mg daily) and developed hallucinations, dysarthria, and incoordination, reversed by physostigmine after several days (117). Therapeutic dosages have been associated with deaths in adults. A 60-year-old woman was started on amitriptyline for depression at a dosage of 25 mg three times daily for 2 weeks (in addition to phenobarbital, chlorpromazine, and other drugs). When the dosage was increased to 50 mg three times daily, she developed abdominal distention, paralytic ileus, and cardiovascular collapse and died (113).

Clomipramine

There were two level 2b trials in which clomipramine was given prospectively and in which toxic effects developed (118,119). The lowest dosage of clomipramine associated with toxicity in adults was 150 mg/day (119). In a level 2b open-label trial of clomipramine given for the treatment of autism with movement disorders, three of five children aged 7–12 years on dosages of 3.9–9.8 mg/kg/day developed agitation and aggression requiring hospitalization. Symptoms abated upon discontinuation of the drug. The authors recommended that children should not receive doses of clomipramine greater than 3–5 mg/kg/day (118).

Desipramine

There were several articles identified in which desipramine was given prospectively, resulting in toxic effects. In a level 1b prospective trial, dosages of 100–200

mg/day were associated with a mean increase in heart rate and various ECG intervals (108). Rapoport et al. (120) described a prospective study of 20 boys with enuresis given 75 mg desipramine nightly for 24 days who reported higher rates of dry mouth and daytime drowsiness than placebo-treated controls. Schroeder et al. (121) studied 20 children taking desipramine titrated to a maximum daily dose of 5 mg/kg (average dose 4.25 mg/kg) for eating disorders, ADD, or affective disorders and found an 18% increase in heart rate and 9% increase in QTc interval on ECG at 8 weeks into the study, neither of which was clinically significant. However, seven of 20 children did not reach the maximum dosage.

There were also two level 4 retrospective case series (122,123) and several case reports. Wagner and Fershtman (124) described a 12-year-old boy diagnosed with depression taking desipramine (2.5 mg/kg/day) who developed symptomatic QTc prolongation (9.7% increase over his baseline) during 2 months of therapy. Varley and McClellan (105) reported the sudden deaths of two children—a 9-year-old 5 weeks after starting desipramine (3.3 mg/kg/day) for depression and a 7-year-old taking a combination of imipramine (6 mg/kg/day) and thioridazine (1 mg/kg/day) chronically for a conduct disorder. A 2001 report by Varley (125) identified eight cases of sudden death during TCA use in children, including six deaths related to desipramine. A level 4 case series of three deaths involved children 8 (two cases) and 9 years of age taking desipramine (50 mg daily for one and unknown dosages for the other two) for periods ranging from 4–6 weeks to 2 years as therapy for attention deficit hyperactivity disorder (ADHD, two cases) or depression. Serum despiramine concentrations were only 10 μg/L (two cases) and 85 μg/L (123). A fourth case reported later was a 12-year-old girl with ADHD. Her dosage of desipramine was raised from 125 mg daily taken during the preceding 6 months to 150 mg daily in divided doses; she was found unconscious a few days after the dosage change and died (126).

Doxepin

There were two level 2b prospective trials in which toxic effects developed when doxepin was given (111,112). Between them, dosages as low as 150 mg/day were associated with a higher mean heart rate, and dosages of 200 mg/day were associated with ST-T changes on ECG. There was also a level 4 case series in which one patient developed convulsions while taking 250 mg/day of doxepin (122).

Imipramine

There were nine articles in which toxicity developed when imipramine was given prospectively. Three of these were level 1b (120,127,128) and six were level 2b (99,109,112,129–131). Among these prospective trials, the lowest dosages of imipramine associated with toxicity were 50–200 mg/day, which were associated with agitation, flushes, and insomnia (129). In one prospective study of 22 children aged 5–17 years, imipramine titrated to a maximum dosage of 5 mg/kg/day in divided doses produced increases in the QRS complex duration on ECG in 19 children and a 10% drop in standing systolic blood pressure in three (130). Rapoport et al. (120), in a prospective, placebo-controlled study of 20 boys ages 7–12 years old with enuresis treated with 75 mg imipramine nightly for 24 days, reported increased rates of daytime drowsiness, headache, and dry mouth with imipramine.

There was also one level 3b study (95) and two level 4 retrospective case series (122,132) along with 16 individual cases of chronic imipramine toxicity in nine level 4 articles (96,105,110,133–138). Bartels et al. (95) reviewed the ECGs of 39 children and adolescents before and after starting imipramine or desipramine therapy (mean maintenance dosages of imipramine and desipramine were 3 and 2.9 mg/kg/day, respectively) and found increases in the PR intervals of 11 patients and new first-degree AV block in two patients. In another report, two children, aged 6 and 8 years with hyperactivity, developed new-onset convulsions after taking imipramine (75 mg three times daily) for weeks to months (96). The lowest dosage associated with toxicity in an adult was 75 mg/day, resulting in syncope, bradycardia, and asystole after 5 days of therapy in a 37-year-old man. However, he was on other medications and had a history of glomerulonephritis, hypertension (treated with guanethidine and methyldopa), and congestive heart failure (138).

Nortriptyline

There were five articles in which nortriptyline was given chronically and in which toxic effects developed. Four of these were level 2b (65,112,139,140) and one was a letter to the editor describing an unpublished study in which dosages of 50–150 mg/day were associated with cardiac conduction defects (141). Two level 4 case reports described chronic nortriptyline toxicity after 2–5 doses of 200 mg/day (142).

Trimipramine

There were two articles in which toxic effects developed when trimipramine was given chronically. One of these was a level 1b quality randomized trial (94) and the other was a level 2b trial (109). Dosages of 50 mg/day were associated with minor adverse effects including nausea, vomiting, drowsiness, and rash (94).

ECG diagnosis

Analyses of ECG changes early in TCA poisoning have been undertaken in order to attempt to predict the risk of life-threatening cardiovascular or neurological complications. In a 5-year retrospective study (level 2b) of 225 TCA overdoses admitted to an intensive care unit, Hulten and Heath (143) found that patients with QRS durations longer than 100 msec were more likely to develop respiratory depression,

convulsions, and death. Boehnert and Lovejoy (144) carried out a level 2b prospective observation study of 49 patients with acute TCA poisoning presenting within 16 hours of their overdoses. The 36 patients whose QRS durations exceeded 100 msec had a higher risk of developing convulsions or arrhythmias. Niemann et al. (145) studied 11 patients with confirmed TCA poisoning (level 2b) and found that the terminal 40 msec vector on the ECG was the best predictor of toxicity, although both QRS duration and QTc duration were also abnormal. Wolfe et al. (146) reviewed (level 2b) the records of patients with TCA (N = 48) versus other poisoning (N = 30) and found that a terminal 40 msec axis of 120–270 degrees on the ECG had the highest sensitivity (83%) and specificity (63%) in predicting TCA toxicity. Liebelt et al. (147), in a prospective cohort study (level 2b) of 79 TCA overdoses reported to one poison center, found that an R-wave greater than 3 mm in lead aVR of the ECG was predictive of both convulsions and dysrhythmias with better sensitivity (81%) and specificity (73%) than either the serum TCA concentration or QRS duration. A recent systematic review (level 2a) included 18 studies of the predictors of clinical severity (arrhythmias, convulsions, or death) in TCA poisoning. QRS duration and blood concentration had only fair sensitivity (0.69 and 0.75) and specificity (0.69 and 0.72) in predicting convulsions and similar sensitivity (0.79 and 0.78) and worse specificity (0.46 and 0.57) in predicting arrhythmias (148). The panel determined that ECG results are available from EMS personnel to some poison centers and chose to consider this parameter for the recommendations offered in this guideline.

Onset of effects and duration of monitoring

Panel members expressed interest in taking into account the time for toxicity to develop after TCA exposures, in order to help make decisions about prehospital transportation and management. All articles were searched for evidence documenting or estimating a time of onset. Unfortunately, the vast majority reported times of presentation to healthcare facilities but not times of symptom onset, which might have occurred earlier. Thus, in most cases, it was only possible to establish an upper limit of time to onset. Care had to be taken when evaluating these articles not to confuse onset of any adverse effects with onset of serious or major effects, time to peak effects, or the occurrence of delayed effects or deterioration. Decontamination measures might have affected times of onset of symptoms. It was often not clear whether, or what, symptoms were present before the late-occurring events emphasized in the reports. There were few data to distinguish time of onset by patient age or by individual TCA.

Delayed clinical deterioration

Many patients who developed clinical effects of TCA poisoning went on to develop more serious effects later. Those who did experience significant deterioration tended to do so quite rapidly, indeed catastrophically in some cases. For example, Ellison et al. (54) reviewed the charts of 30 patients who experienced convulsions after TCA overdose (level 4). Convulsions started within 1½ hours of admission in 28 of 30, 23% had been fully alert just prior to the convulsion, and 10% died. Patients in other reports deteriorated progressively over the course of hours to days after the ingestion (50,66,68,85,92,149–152). There were also several level 4 reports of delayed toxicity (especially conduction defects or dysrhythmias) or even death after a period of relative improvement or stabilization (2,52,66,92,153–155). It is unclear whether the delayed effects represented recurrence of direct TCA toxicity (e.g., due to ongoing absorption, inadequate decontamination, mobilization of tissue stores) or secondary complications of hospitalization or treatments (e.g., aspiration of gastric contents, adult-type respiratory distress syndrome), other co-ingestants or co-medications (e.g., acetaminophen toxicity, alcohol withdrawal), or a different pathophysiologic process (e.g., serotonin syndrome, intestinal obstruction, neuropathy due to TCA effects). In some cases, this deterioration occurred days after the ingestion; however, in all cases, significant initial toxicity had been previously documented.

Time of onset

In most cases, the time of effect onset, when noted, appeared to be within 2 hours after the TCA ingestion. However, in some, effects did not appear for several hours. Effects were reported up to 5 hours after amitriptyline or nortriptyline ingestion in one level 1b therapeutic trial (57).

A 7-year, level 2b review of 88 TCA poisoned patients found that none developed hemodynamic complications after 12 hours following ingestion (56). A level 4 retrospective case series of 60 childhood poisonings involving amitriptyline and imipramine reported that symptoms usually developed within 4 hours of ingestion (38). The longest documented time to onset of toxicity was 6 hours after an ingestion of imipramine by a young child (50). In one report (level 4), a 4-year-old boy with enuresis drank 90 mL imipramine syrup (32 mg/kg), was given a salt-water mixture by his mother, vomited, "went to sleep," and 4 hours later developed convulsions and then ventricular tachycardia and fibrillation (150). A 44-year-old man taking 75 mg amitriptyline daily for months to treat depression ingested 750 mg and presented to an emergency department 16 hours later with only drowsiness as a symptom of toxicity (155).

A description of 111 TCA overdose-related deaths (level 4) reported to a coroner's office reported that most patients developed major signs within 3 hours of hospital presentation. Two patients had cardiac arrests more than 3 hours after presentation; however, the presenting signs and at what time they arrested were not detailed in the article (3). In a level 2b review of 102 adults admitted with TCA overdose, the first manifestation of convulsions and ventricular dysrhythmias occurred within 6 hours of admission in all patients (156). In

another level 2b prospective observational series of 49 patients, all convulsions and dysrhythmias occurred within 6 hours of ingestion (144). In a level 2b prospective observational series of nine adults with severe amitriptyline poisoning, the onset of all convulsions, dysrhythmias, and hypotension occurred within 4 hours of admission (157).

Duration of symptoms

In a level 4 prospective case series of 24 adults admitted with TCA overdose, two patients developed transient supraventricular tachycardia 2–4 days after ingestion (92). In a retrospective review of 316 patients admitted with TCA overdose (level 4), hypotension and convulsions more than 24 hours after ingestion were unusual but occurred in two patients and one patient, respectively (158). In a level 3b observational series of 40 patients with TCA overdoses, all major effects occurred within 24 hours of ingestion (40). Similarly, in a level 2b study of 72 patients admitted with TCA overdose, all clinical effects, with the exception of aspiration symptoms, developed within 24 hours of ingestion (83). In a level 4 case series of 62 adults admitted with TCA overdose, none developed a new dysrhythmia after 24 hours (159). In a level 3b report of 40 patients admitted with TCA overdose, maximal clinical effects and TCA concentrations developed within 24 hours in all patients except one who was on a corticosteroid for a neurological disorder at the time (160). In a description (level 4) of 45 patients hospitalized for TCA overdose (60% of whom presented within 6 hours of the ingestion) no complications occurred after 24 hours. Of note, one patient presented without any major signs or symptoms but within 6 hours of presentation was comatose (161).

A report (level 4) of 24 adults with convulsions after TCA overdose found that the onset of convulsions occurred within 18 hours in all patients (6). In a level 4 retrospective review of 30 patients admitted with convulsions after TCA overdose, the onset of convulsions ranged from 0.5 to 9.3 hours. Many of these patients had decreased levels of consciousness prior to convulsion onset but 23% were awake at the time. Whether other effects were present in these patients—clinically or electrocardiographically—is not clear (54). In a level 2b review of 72 adults admitted to an ICU with TCA overdose, only one patient developed a new ECG abnormality after admission (162). A larger level 4 retrospective review of 295 patients admitted to one ICU with TCA overdose found that multiple patients developed convulsions, circulatory impairment, or ECG abnormalities after admission (48). In a 3-year, level 2b retrospective review of 75 hospitalized patients with TCA overdoses, Goldberg et al. (83) found that none of those who had not aspirated developed any serious new toxicity more than 24 hours after ingestion. In a level 4 retrospective review of 38 patients hospitalized for TCA overdoses, all ECG changes normalized within 24 hours. The authors suggested that patients fully recovered from TCA-related ECG changes need be monitored only for 12 hours (163).

Emerman et al. (164) performed a 10-year, hospital-based, level 2b review of the records of 92 adults with TCA overdose and found that their initial level of consciousness (Glascow Coma Scale <8: 86% sensitivity, 89% specificity) best predicted the 37 patients (40%) who developed serious complications—73% developed complications within 30 minutes of presentation to the emergency department and none developed new complications more than 2 hours after arrival at the hospital. In a prospective study of 67 patients, Foulke (165) concluded that high-risk features predicting late complications included QRS duration, the presence of arrhythmias or conduction delays on ECG, altered mental status, convulsions, respiratory depression, or hypotension.

Duration of monitoring of asymptomatic patients

The duration of monitoring recommended varies for treated patients with TCA poisoning. Foulke et al. (156) reviewed 165 TCA overdoses (level 2b) and found that patients without major evidence of toxicity in the emergency department did not develop serious complications later. Pentel and Sioris (166), in a level 4 review of 129 adults with TCA overdoses, found that all who developed neurological or cardiovascular complications did so within 1 hour of their admission. In their survey of 30 poison centers, McFee et al. (35) found that all recommended a monitoring period at least 6 hours; one recommended 6–12 hours and two recommended 24 hours. In a review of TCA poisoning, Callaham (167) suggested that asymptomatic, decontaminated patients should be monitored for at least 6 hours (but this would be 6 hours after presentation to a healthcare facility, not 6 hours after the ingestion). Later, Callaham and Kassel (3) studied 111 TCA-associated deaths and concluded that 6 hours is an adequate time to monitor decontaminated patients for the development of major signs of toxicity. Others have also recommended a 6-hour observational period for symptoms after decontamination measures have been taken (161). Banahan and Schelkun (168) reviewed 33 cases of TCA overdose (level 4) and concluded that a 6-hour observational period can avert the cost of unnecessary hospitalization.

Underlying medical conditions/special populations

Patients with underlying heart disease or cardiac arrhythmias or conduction disturbances could be especially sensitive to the toxic effects of TCAs (169). Those with underlying seizure disorders and taking TCAs could experience a lowering of the seizure threshold (170). TCAs can interact with many different medications, including other psychopharmaceuticals such as MAO inhibitors. It is reasonable to assume that patients taking other drugs (e.g., cardioactive agents like digitalis, calcium channel blockers, or ß-blockers) who overdose on TCAs might have increased risks of toxicity such that they require immediate triage to a healthcare facility for monitoring.

Prehospital management of TCA Poisoning

There were few level 1, 2, or 3 articles specifically addressing out-of-hospital management of TCA exposures (although many articles contained some limited out-of-hospital information). It was felt that some in-hospital data could be utilized to develop out-of-hospital guidelines. Therefore, both in- and out-of-hospital data are included in this review of the evidence. While physostigmine, phenytoin, and ß-blockers have been used to treat TCA poisoned patients in the past, these agents are not used routinely in the current management of TCA poisoned patients (19). Moreover, the panel determined that some hospital-based therapies such as glucagon and hyperventilation would not be included in this guideline.

Gastrointestinal decontamination

Only decontamination measures that could reasonably be expected to be available and carried out in a prehospital setting and which had a significant amount of data are reviewed here.

Ipecac-induced emesis

There were no controlled trials of the use of ipecac syrup for TCA overdose and no prospective volunteer studies examining the efficacy of ipecac in reducing TCA absorption even after therapeutic doses. There were multiple case reports in which ipecac syrup was administered after suspected TCA overdoses (68,161,166,171–174). In some of these, tablets or tablet fragments were recovered (68,166). However, most did not test the recovered fragments to confirm their identity, nor did they quantify how much of the ingested dose was recovered. These limitations, coupled with the rare reports of adverse events as a result of ipecac syrup administration, make the value of these individual reports questionable.

Activated charcoal

Tricyclic antidepressants are adsorbed by activated charcoal. Crome et al. (175) demonstrated that 1 g of activated charcoal adsorbed 318 mg nortriptyline in an in vitro model. Activated charcoal might be effective in decreasing the absorption of TCA if given early enough after ingestion.

Investigations of activated charcoal's effectiveness in studies performed using TCA poisoned patients have yielded mixed results. There were several level 2–3 articles in which activated charcoal was used in an uncontrolled fashion but in which its efficacy was not reported. In addition, there were numerous level 4 case reports or series in which single or multiple doses of activated charcoal were given to individuals with TCA overdoses, but it was impossible to determine the efficacy of activated charcoal from these reports given the lack of controls, the concurrent use of other therapies, the fact that activated charcoal does not produce immediate clinical improvement (i.e., outcome is generally measured by improved pharmacokinetic parameters or the prevention of later clinical sequelae), and that the interval between the time of TCA ingestion and administration of charcoal is often unknown. For many studies of TCA poisoned patients given activated charcoal in emergency departments, the delay in its administration for many hours beyond the time of TCA ingestion might account for an observed lack of effectiveness.

A level 1b, randomized, controlled trial investigated three decontamination methods in 51 adults with acute unspecified TCA overdose. There were no significant differences in any of the outcome measures (clinical and laboratory) between patients receiving activated charcoal 50 g with magnesium citrate (group 1), patients receiving gastric lavage followed by activated charcoal 25 g with magnesium citrate (group 2), or those receiving activated charcoal 25 g followed by gastric lavage followed again by activated charcoal (group 3). However, there were no untreated controls so the effectiveness of charcoal could not be established (176).

A level 1b, prospective randomized trial in 77 patients admitted with acute TCA overdose compared the efficacy of gastric lavage alone vs. gastric lavage plus activated charcoal 20 g. Patients randomized to the activated charcoal group had no significant differences in peak TCA serum concentration, drug half-life, or AUC when compared to the gastric lavage-only patients. Slightly fewer patients in the activated charcoal group developed convulsions, hypotension, or dysrhythmias or required prolonged intubation, ICU care, or hospitalization, but these trends did not reach statistical significance (177).

A level 2b study of 48 children less than 6 years of age who had been reported to one poison center after acute TCA exposure found that there was no difference in clinical outcome between those who had received activated charcoal and those who had not. However, there were no cases of significant toxicity in any of the patients, and some patients had also received gastric lavage and/or a cathartic (46).

Hedges et al. (178), in a level 2b, prospective study of nine adults with acute TCA poisoning, detected a correlation between the time to activated charcoal administration (along with gastric lavage and supportive care) and reduced serum half-life of the TCA and an inverse correlation between the dose of activated charcoal given and drug half-life. In a level 1b study, Crome et al. (179) randomized 48 patients with suspected acute TCA overdose to receive either supportive care alone or supportive care plus activated charcoal 10 g and detected no differences in clinical outcome or the rate of fall of serum concentrations.

In addition to the above studies, there were several articles that looked at the effect of activated charcoal on TCA absorption in volunteers given relatively low doses of various antidepressants. In a level 1b study, a single 5-g dose of activated charcoal given 30 minutes after a 75-mg dose of nortriptyline reduced its mean peak serum concentration by 60% in 12 healthy adult volunteers (175). A level 2b, prospective, crossover trial in six adult volunteers who ingested 75 mg nortriptyline compared the efficacy of single- and multiple-dose activated charcoal in reducing nortriptyline absorption (180).

Subjects given activated charcoal (amount not reported) at 30 minutes had a 58% mean reduction in peak nortriptyline serum concentrations and a 55% mean reduction in overall bioavailability. A similar level 1b, prospective, crossover trial in six adult volunteers compared the efficacy of activated charcoal when administered at various times after 75 mg doses of nortriptyline. Activated charcoal 10 g given at 30 minutes after ingestion resulted in a 77% reduction in mean peak nortriptyline serum concentration and a 74% reduction in overall bioavailability; the same dose given at 2 hours resulted in 37% and 38% reductions, respectively; and, when given at 4 hours, resulted in reductions of 19% and 13% (181).

A level 1b, prospective, multi-phase, crossover trial in six volunteers looked at the effects of various interventions on amitriptyline pharmacokinetics compared to an untreated control phase after the ingestion of single doses of 75 mg amitriptyline. Single doses of 50 g activated charcoal given 5 minutes after amitriptyline prevented the drug's absorption (as measured by peak serum concentration, AUC, urinary excretion, and drug half-life) by 99%. Multiple doses of activated charcoal beginning at 6 hours after ingestion were much less effective but still reduced amitriptyline's peak serum concentration, half-life, AUC, and urinary excretion (58). A self-controlled, level 2b trial of doxepin 50 mg given to eight adult volunteers followed either by a single 15-g dose of activated charcoal 30 minutes later or multiple doses of activated charcoal over 24 hours (given at 3, 6, 9, 12, and 24 hours after ingestion) found reduced doxepin AUC after both interventions compared to controls, but only multiple doses improved the clearance of doxepin (76). An expert panel convened by the American Academy of Clinical Toxicology and the European Association of Poison Control Centres & Toxicologists recommended that single-dose charcoal be considered if a patient has ingested a potentially toxic amount of a poison up to 1 hour previously, noting that there are insufficient data to support or exclude its use after 1 hour (182).

Although the prehospital administration of activated charcoal by emergency medical service personnel has been proposed (183–185), there are no studies of its safety or utility specifically in TCA poisoning. There are important concerns about the potential for complications when using activated charcoal in this context. Instillation of activated charcoal through an orogastric or nasogastric tube in a comatose patient can be a source of iatrogenic injury. Godambe et al. (186) described the case of a 13-year-old girl who, after lapsing into coma following a multi-drug overdose including amitriptyline, had pleuropulmonary activated charcoal instillation from a nasogastric tube, which entered the left mainstem bronchus and then extended into the parenchyma and through the visceral pleura. TCA poisoned patients have aspirated activated charcoal, resulting in severe complications or death (88). Roy et al. (187) studied 82 consecutive TCA poisoned patients admitted to an intensive care unit and found evidence of aspirated activated charcoal in the airways of 18 of 72 (25%) patients who required intubation, although their survival rate did not differ from that of those who had not aspirated (level 4). The authors did not state how many patients, if any, had received charcoal prior to arrival at the emergency department.

There are also case reports (level 4) of patients suffering ileus, toxic megacolon, bowel obstruction, or intestinal ischemia after TCA poisoning (188,189). In such patients, administration of any oral medication, including charcoal, would be contraindicated. Gomez et al. (190) reported a 39-year-old woman who developed an activated charcoal stercolith and intestinal perforation requiring surgery during treatment of an amitriptyline poisoning. A 21-year-old man presented with coma and convulsions related to amitriptyline poisoning, received multiple doses of activated charcoal (with atropine, lidocaine, defibrillation, gastric lavage, and other therapies), and developed intestinal obstruction from inspissated activated charcoal requiring surgery (191).

Other treatment measures

There are many different prehospital treatment measures for TCA overdose reported in the literature including intubation, intravenous fluids, and typical supportive measures such as oxygen, atropine, glucose, naloxone, antiarrhythmics, CPR, defibrillation or cardioversion, and military anti-shock trousers. Anticonvulsants (e.g., diazepam) could be indicated for patients who have sustained convulsions or are exhibiting physical signs of an impending convulsion such as hyperreflexia, change in consciousness, tremors, and myoclonus. None of these have controlled prehospital studies specific to TCA overdoses. Since they are already routinely used in the prehospital setting, the anecdotal data are not presented here.

Sodium bicarbonate

There is considerable evidence in both animal and human studies that alkalinization of the blood can be beneficial in the management of TCA poisoning. In a rat model, sodium bicarbonate increased the survival rate of animals poisoned experimentally with amitriptyline and its benefit was additive to that of an inotropic agent such as epinephrine or norepinephrine (192). An expert panel convened to consider ACLS measures after TCA poisoning recommended alkalinization with hypertonic solutions of sodium bicarbonate (193).

In a 1976 level 4 case series, 11 of 12 children with TCA-induced arrhythmias responded to intravenous sodium bicarbonate with conversions to normal cardiac rhythm (194). In a level 2b review of 184 patients admitted to an ICU after amitriptyline overdose, four of eight patients treated with bicarbonate had improvements in cardiac conduction (60). A level 2b, retrospective cohort analysis compared the outcomes of 91 patients with TCA overdose who received bicarbonate with those of 24 patients who did not. While there was no direct statistical comparison between treated and untreated groups, hospital stay was shorter for the treated group. Furthermore, within the bicarbonate group, 20 of 21 patients

with hypotension had improvements in blood pressure, 39 of 49 patients with QRS prolongations had narrowing of their QRSs, 40 of 85 patients with altered mental status had improvements in consciousness, and 42 of 43 patients had improvements in acidosis. There were no complications from bicarbonate (195). Urinary acidification with ammonium chloride or urinary alkalinization with bicarbonate, beginning 1 hour after the ingestion of 75 mg amitriptyline, resulted in a cumulative excretion of less than 5% of the ingested dose over 72 hours (58).

There are numerous cases or case series (level 4) in which patients with TCA overdoses apparently responded favorably to sodium bicarbonate (improved vital signs, cessation of dysrhythmias or convulsions, reduction in acidosis, and/or improved cardiac conduction) in a temporally consistent manner (22,23,54,89,90,96,149,152,154,158,171,196–214). In other cases, bicarbonate was given either without improvement or with an unreported response (3,43,82,92,154,173, 174,197,209,212,213,215–223). There were also cases in which bicarbonate might have resulted in or contributed to adverse effects (e.g., pulmonary edema or excessive alkalemia) (75,82,202). Other reports used other forms of alkalinizing therapy (e.g., sodium lactate) or unspecified alkalinization procedures. In some cases these were beneficial but not in others (6,41,44,224).

Intravenous fluids

Intravenous fluids, lidocaine, and respiratory support were all found to be helpful in stabilizing blood pressure and the cardiopulmonary status of TCA-poisoned patients in retrospective level 4 case series (44,225).

Flumazenil

The administration of flumazenil to comatose patients with unknown poisonings, as both a diagnostic and therapeutic measure, has occasionally resulted in the unmasking of convulsions in TCA-poisoned patients who had co-ingested benzodiazepines (226).

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.

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 a patient with tricyclic antidepressant ingestion. These variables include the patient's intent, the time of the ingestion, the patient's symptoms, any underlying medical conditions, the dose of the specific product ingested, and any co-ingested drugs. The expert consensus panel agreed that in each case, the judgment of the specialist in poison information or the poison center medical director or other poison center clinicians might override any specific recommendation from this guideline.

Patient intent

The expert consensus panel concluded that all patients with suicidal intention or in whom a malicious intent is suspected (e.g., child abuse or neglect) should be transported expeditiously by EMS to an emergency department. Patients without these characteristics are candidates for consideration of prehospital management of their TCA ingestion.

Time since ingestion

The expert consensus panel concluded that decisions about referral to an emergency department should be based on the clinical status of the patient within the first 6 hours after TCA ingestion. The panel concluded that an asymptomatic patient who unintentionally ingested a TCA is unlikely to develop symptoms if the interval between the ingestion and the call is greater than 6 hours. Patients with unintentional TCA poisoning who are more than 6 hours after ingestion at the time of the first contact with a poison center and are still asymptomatic can be safely monitored at home.

Patient's symptoms or underlying medical conditions

The expert consensus panel concluded that referral to an emergency department should be considered for any patient who is experiencing symptoms that might be reasonably related to the TCA (e.g., dizziness, syncope, convulsions, chest pain, generalized weakness, shortness of breath), who has severe underlying neurological (e.g., epilepsy) or cardiovascular disease (e.g., end-stage cardiomyopathy), or who is

on multiple psychopharmaceutical or cardiovascular medicines that could have additive neurological or cardiodepressant effects with the TCA. The importance of each of these variables can be difficult to judge in a telephone conversation so a low threshold for emergency department evaluation is considered prudent. Symptomatic patients should be transported by EMS.

Dose of the drug

The panel concluded that a specific toxic dose of TCA to trigger referral to an emergency department has limited support of evidence in medical toxicology textbooks, TESS fatality information, or the medical literature. The panel recognized the risk of serious complications after TCA poisoning at relatively low doses in both children and adults. The panel noted that it is widely believed among poison centers that older children and adults are much more likely to have suicidal or homicidal intent. It concluded that the severity of poisoning that occurred secondary to self-harm, intentional misuse, Munchausen-by-proxy, child abuse, or other malicious intent appeared to result in more severe outcomes (e.g., fatalities) compared to unintentional ingestion. This is likely to be a consequence of larger dose and delayed time to treatment. There is no evidence that age alone influences the outcome.

The estimation of dose is based largely on the patient's history and the type of product and its packaging (when available for evaluation). If precise data for the ingestion are unknown or unclear (package size, unit size, number of units ingested), poison centers in the US often utilize a method in which the maximum potential dose is calculated.

For asymptomatic patients with acute, unintentional ingestions of TCAs, the expert consensus panel concluded that home observation might be allowable for very small exposures. However, the panel recognized that a definite threshold dose for toxicity, based on a confirmed history of exposure, has not been established. After a thorough review of published case reports, recommended therapeutic dosage regimens, current poison control center practices, and expert experience, the panel concluded that ingestion of either of the following amounts, whichever is lower, should 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.

Based on this principle, the panel determined that more than 5 mg/kg should be the minimal dose for referral to an emergency department, except in the cases of desipramine (>2.5 mg/kg), nortriptyline (>2.5 mg/kg), trimipramine (>2.5 mg/kg), and protriptyline (>1 mg/kg). These doses are extrapolated back from the maximum therapeutic adult doses shown in Table 2. 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, when added to the daily dose taken, should then be compared to the threshold dose for referral to an ED.

There is support for this threshold dose in retrospective studies (45–47) that reported little significant toxicity in doses less than 5 mg/kg, in case reports of minimal doses associated with sigificant toxicity (Tables 4 and 5), in toxicology textbooks that often define 10 mg/kg (or 1000 mg) as the dose above which significant toxicity is seen, in prospective therapeutic dosing studies (95,95,112,121,130), and in a meta-analysis in which mean dosing to 3 mg/kg daily of a TCA (2 mg daily for nortriptyline) has been administered routinely therapeutically to older children and adults with few significant side effects (106). However, it also acknowledges recent work showing a comparatively higher case fatality rate attributable to desipramine exposures compared with other TCAs, which supports a lower threshold dose of concern (12,13). This conclusion acknowledges that rare, idiosyncratic reactions to TCAs, including cardiac arrest, have occurred in patients taking only therapeutic doses. The panel also concluded that the toxic dose of doxepin cream preparation, when ingested, could not be established from the evidence and so chose to assign the same 5 mg/kg threshold for referral to an emergency department as oral doxepin dosage forms.

The panel recognized that the decision to send a patient to an emergency department for monitoring is made on a case-by-case basis, taking into account the reliability of the caller's history, underlying medical status, concomitant use of other medications (e.g., psychopharmaceutical or cardioactive agents) that could have additive neurotoxicity or cardiodepressant effects, and other variables.

Duration of observation for asymptomatic patients

The expert consensus panel concluded that onset and duration of toxicity were clearly affected by several variables including the total quantity ingested, co-ingestants, and gastrointestinal decontamination measures such as activated charcoal. Other factors, such as type of pharmaceutical product (e.g., capsule vs. tablet) and the presence or absence of food in the stomach could also affect the time of onset and duration of toxicity; however, no studies were found that addressed such differences directly. After a careful review of the case reports and observational studies, and considerable discussion, the panel concluded that a patient with normal sensorium who is asymptomatic 6 hours after ingestion of a TCA is unlikely to subsequently develop significant symptoms.

Potential out-of-hospital management

The expert consensus panel concluded that close monitoring of vital signs, respiratory, cardiovascular, and neurological status of patients with possible severe TCA poisoning is of critical importance. When possible, ECG monitoring should also be included.

Gastrointestinal decontamination

The expert consensus panel concluded that out-of-hospital gastrointestinal decontamination offered potential benefit, but that the magnitude of the benefit and the risks for the patient were difficult to determine. Inducing emesis with ipecac syrup was concluded to carry a major risk of pulmonary aspiration of gastric contents if the patient became hypotensive or lost consciousness and is not supported by sufficient evidence of benefit to warrant its use. Moreover, ipecac syrup would likely delay or prevent the use of activated charcoal. It might induce a vagal stimulus that could further depress the heart rate and trigger life-threatening arrhythmias. The panel concluded that ipecac syrup is contraindicated in TCA poisoning.

Activated charcoal was determined by the panel to be a treatment that could be administered orally as part of the management of a TCA-poisoned patient, although its effectiveness and risks have not been evaluated in the prehospital setting. Aspiration of activated charcoal, with subsequent pulmonary complications, is a considerable risk of its administration to TCA-poisoned patients whether in the prehospital or hospital setting. It cannot be recommended for routine prehospital management of TCA poisoning at this time, although it might be considered in some regions in which prehospital activated charcoal is routinely administered by emergency medical personnel and there is a long transportation time to an emergency department. Also, the panel agreed that transportation to an emergency department should not be delayed in order to attempt activated charcoal administration.

Specific pharmacological therapy

The expert consensus panel concluded that intravenous fluids would likely be necessary in the prehospital care of hemodynamically unstable TCA-poisoned patients. Although the available literature on in-hospital management of TCA poisoning supports the use of intravenous sodium bicarbonate, which is often available to paramedics, no studies were found addressing the effectiveness or safety of this drug for the out-of-hospital treatment of TCA-induced hypotension and arrhythmias. However, standard ACLS doses of sodium bicarbonate can be considered for prehospital patients found to have life-threatening hypotension and cardiac conduction disturbances evident on an ECG or rhythm strip. The panel concluded that flumazenil is contraindicated if there is any possibility that a comatose patient may have ingested a TCA.

Recommendations *(grades combined where appropriate)*

1. Patients with suspected self-harm or who are the victims of malicious administration of a 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 EMS, 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 mg/kg. For despiramine it is >2.5 mg/kg; and for nortriptyline it is >2.5 mg/kg; for trimipramine it is >2.5 mg/kg; for protriptyline it is >1 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 (Grades 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 ECG 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 ACLS guidelines as outlined by the American Heart Association (227) (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.

Implications for research

The expert consensus panel identified the following topics where additional research might be useful.

1. A prospective study of the dose of acute pediatric TCA ingestion requiring observation at a healthcare facility could help to reduce unnecessary utilization of healthcare resources.
2. A large-scale, prospective study of unintentional TCA ingestions is needed.
3. An additional need is a better correlation between the estimated ingested dose, clinical symptoms, and outcome in patients with serious overdoses.
4. Research is needed into the adverse effects of TCAs in pregnant women.
5. The efficacy and safety of prehospital decontamination with activated charcoal for TCA poisoning is unknown and merits investigation.
6. The efficacy and safety of glucagon, sodium bicarbonate, or other measures given in a prehospital setting for the treatment of TCA poisoning is unknown.

Disclosures

Dr. Booze's husband is employed by AstraZeneca. Dr. Erdman is currently employed by Genentech 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.

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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

Algorithm for triage of tricyclic antidepressant ingestion

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 symptomatic? (e.g., weak, drowsy, dizzy, tremulous, palpitations)	YES → Refer to emergency department.
NO ↓	
Have more than 6 hours elapsed since the TCA ingestion and the patient is still asymptomatic?	YES → Continue to follow closely at home.
NO ↓	
Does the patient have significant underlying cardiovascular or neurological disease, or is he/she taking a cardiodepressant drug or MAO inhibitor?	YES → Consider referral to emergency department.
NO ↓	
Can you estimate the maximum amount ingested?	NO → Refer to emergency department.
YES ↓	
Has the patient ingested a potentially toxic dose?* Amitriptyline >5 mg/kg Clomipramine >5 mg/kg Desipramine >2.5 mg/kg Doxepin >5 mg/kg Doxepin cream† >5 mg/kg Imipramine >5 mg/kg Nortriptyline >2.5 mg/kg Protriptyline >1 mg/kg Trimipramine >2.5 mg/kg	YES → Refer to emergency department.
NO ↓	
Observe at home. Instruct caller to call poison center back if symptoms appear. Consider poison center-initiated follow-up within 4 hours of initial call. Consider referral to emergency services should new symptoms develop.	

*Algorithm applies only to ingested TCAs, not to parenteral use or other routes of exposure. Algorithm applies only to acute ingestions.
†A toxic dose for dermal exposures could not be established from available evidence. The dose represents the ingestion of a dermal preparation.