



Complete Summary

GUIDELINE TITLE

Selective serotonin reuptake inhibitor poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Nelson LS, Erdman AR, Booze LL, Cobaugh DJ, Chyka PA, Woolf AD, Scharman EJ, Wax PM, Manoguerra AS, Christianson G, Caravati EM, Troutman WG. Selective serotonin reuptake inhibitor poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 May;45(4):315-32. [107 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Selective serotonin reuptake inhibitor (SSRI) poisoning

Notes:

- The following pure SSRIs are subjects of this guideline: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft).
- A number of other agents are also available that have among their pharmacologic properties the ability to inhibit serotonin reuptake. These include bupropion, duloxetine, mirtazapine, and venlafaxine. Given their

pharmacologic complexity and distinction from SSRIs, they are not included in this guideline.

- The guideline applies to ingestion of immediate-release forms of SSRIs; alternative-release mechanisms, particularly sustained-release preparations, are not considered.
- Co-ingestion of additional substances might, but does not necessarily, require different referral and management recommendations depending on the nature of the coingestant(s) and the combined toxicities of the substances.

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

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

GUIDELINE OBJECTIVE(S)

To assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with a suspected ingestion of a selective serotonin reuptake inhibitor (SSRI) by:

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

TARGET POPULATION

Children and adults with suspected selective serotonin reuptake inhibitor (SSRI) poisoning

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision elements for triage
 - Patient intent
 - Patient symptoms
 - Product and dose
 - Time of ingestion and co-ingestants

Management

1. Referral to an emergency department
2. Oral activated charcoal administration
3. Benzodiazepines
4. External cooling measures
5. Home observation
6. Follow-up

Note: Emesis induction was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Mortality
- The threshold dose for the development of toxicity
- Signs and symptoms of toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search

The National Library of Medicine's PubMed database was searched (to March 2004) using serotonin uptake inhibitors (poisoning) or serotonin uptake inhibitors (toxicity) as Medical Subject Headings (MeSH) terms, limited to humans. PubMed was also searched using citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdos* or intox* or toxic*, limited to humans. This process was repeated in International Pharmaceutical Abstracts (1970–March 2004, excluding abstracts of meeting presentations), Science Citation Index (1977–March 2004), Database of Abstracts of Reviews of Effects (accessed March 2004), Cochrane Database of Systematic Reviews (accessed March 2004), and Cochrane Central Register of Controlled Trials (accessed March 2004). A third PubMed search (to March 2004) located all citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline articles that identified patients from 1 through 5 years of age.

Reactions (1980–March 2004), the citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline poisonings in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology (NACCT) abstracts published in the Journal of Clinical Toxicology (1995–2004) were reviewed for original human data. The chapter bibliographies in five major toxicology textbooks were reviewed for citations of additional articles with original human data. Finally, the Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched (2000–2005) for deaths resulting from citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline poisoning. These cases were abstracted for use by the panel.

Criteria Used to Identify Applicable Studies

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 could potentially provide: 1) estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, 2) estimations of time to symptom onset, or 3) information regarding management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that did not meet any of the preceding criteria, did not add new data (e.g., some reviews, editorials), or that described inpatient-only procedures (e.g., dialysis).

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence	Description of Study Design
1a	Systematic review (with homogeneity) of randomized clinical trials
1b	Individual randomized clinical trials (with narrow confidence interval)
1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
2a	Systematic review (with homogeneity) of cohort studies
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

Level of Evidence	Description of Study Design
4	Case series, single case reports (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research
6	Abstracts

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Extraction Process

All articles that were retrieved from the search were reviewed by a trained physician abstractor. Each article was examined for original human data regarding the toxic effects of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline or original human data directly relevant to the out-of-hospital management of patients with these drugs in overdose. Relevant data (e.g., dose of selective serotonin reuptake inhibitor [SSRI], 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 evidence table is available at

<http://www.aapcc.org/DiscGuidelines/Guidelines%20Tables/SSRI%20evidence%20table%202005-6-9.pdf>.

The completed table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Every attempt was made to locate significant foreign language articles and have their crucial information extracted, translated, and tabulated. A written summary of the data was created and distributed by the abstractor. Copies of all of the articles were made available for reading by the panel members on a secure American Association of Poison Control Centers (AAPCC) website.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An expert consensus panel was established to develop the guideline (see Appendix 1 of the original guideline document). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional record in clinical care and scientific research in toxicology, board certification as a clinical or

medical toxicologist, significant US poison control center experience, and be an opinion leader with broad esteem. Two specialists in poison information were included as full panel members to provide the viewpoint of the end-users of the guideline.

Guideline Writing and Review

A guideline draft was prepared by the lead author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, anonymously copied into a table of comments, and submitted to the lead author for response. The lead author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the lead author, the draft was prepared for the external review process.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

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

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

COST ANALYSIS

A published cost analyses was reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (ACMT)

members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (see Appendix 3 in the original guideline document). Comments were submitted via a discussion thread on the AAPCC web site or privately through email communication to AAPCC staff. All submitted comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the lead author. The lead author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

1. All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g., child abuse or neglect) should be referred to an emergency department. This activity should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (**Grade D**).
2. Any patient already experiencing any symptoms other than mild effects (mild effects include vomiting, somnolence [lightly sedated and arousable with speaking voice or light touch], mydriasis, or diaphoresis) should be transported to an emergency department. Transportation via ambulance should be considered based on the condition of the patient and the length of time it will take the patient to arrive at the emergency department (**Grade D**).
3. Asymptomatic patients or those with mild effects (defined above) following isolated unintentional acute selective serotonin reuptake inhibitor (SSRI) ingestions of up to five times an initial adult therapeutic dose (i.e., citalopram 100 mg, escitalopram 50 mg, fluoxetine 100 mg, fluvoxamine 250 mg, paroxetine 100 mg, sertraline 250 mg) can be observed at home with instructions to call the poison center back if symptoms develop. For those patients already on an SSRI, ingestion of up to five times their own single therapeutic dose can be observed at home with instructions to call the poison center back if symptoms develop (**Grade D**).
4. The poison center should consider making follow-up calls during the first 8 hours after ingestion, following its normal procedure. Consideration should be given to the time of day when home observation will take place. Observation during normal sleep hours might not reliably identify the onset of toxicity. Depending on local poison center policy, patients could be referred to an emergency department if the observation would take place during normal sleeping hours of the patient or caretaker (**Grade D**).
5. Do not induce emesis (**Grade C**).
6. The use of oral activated charcoal can be considered since the likelihood of SSRI-induced loss of consciousness or seizures is small. However, there are no data to suggest a specific clinical benefit. The routine use of out-of-

hospital oral activated charcoal in patients with unintentional SSRI overdose cannot be advocated at this time **(Grade C)**.

7. Use intravenous benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia (>104 degrees F [>40 degrees C]) for SSRI-induced serotonin syndrome. This should be done in consultation with and authorized by emergency medical services (EMS) medical direction, by a written treatment protocol or policy, or with direct medical oversight **(Grade C)**.

Definitions:

Grades of Recommendation and Levels of Evidence

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

CLINICAL ALGORITHM(S)

An algorithm is provided in Appendix 4 of the original guideline document for triage for selective serotonin reuptake inhibitor (SSRI) poisoning in patients of all ages.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate out-of-hospital triage and initial out-of-hospital management of patients with suspected selective serotonin reuptake inhibitor (SSRI) poisoning

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the United States. While the toxicities of the selective serotonin reuptake inhibitors (SSRIs) are not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.
- This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions might be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment.

Limitations of the Published Data

As with much of the clinical toxicology literature, there were no prospective studies that specifically investigated toxic dose thresholds for SSRIs, and only a small number of retrospective articles contained any toxic threshold or dose-effect information. Even when such information was presented in an article, there were often questions regarding the accuracy of the dose estimates due to uncertainties in the histories. Among the prospective trials available, the SSRIs were administered in therapeutic doses, which would be much smaller than amounts likely to be ingested in an overdose. Retrospective data with dose-effect information was often confounded by the presence of co-ingestants, differences in decontamination or treatment measures, and concurrent medical conditions that could have altered the clinical presentation or outcome. It was difficult, if not impossible, to account for inter-individual differences in age, weight, underlying health condition and medication use, or genetic factors that might affect an SSRI's toxicokinetics and toxicodynamics. Among larger case series, many of the patients remained asymptomatic and ingested doses and/or effects were typically reported as ranges, percentages, or means for the cases, so that individual doses resulting in specific effects could not be discerned.

Overall, the level 4 and 6 data were extremely difficult to interpret and summarize. The level of clinical detail presented in the case reports and abstracts

varied widely. In most, the SSRI ingestion was not independently verified or confirmed by laboratory testing, nor were co-ingestants adequately evaluated. There is typically poor correlation between estimated doses and subsequent serum concentrations or toxicity, particularly for children with unintentional ingestions of other drugs such as acetaminophen for which quantitative laboratory confirmation is routine. Poison center staff members often knowingly record the dose taken as the worst-case scenario in order to provide a wide margin of safety.

The unclear time interval from ingestion to onset of toxicity is confounded by a lack of a definition for consequential toxicity. For instance, after an SSRI overdose the development of mild drowsiness in a child could indicate the onset of toxicity or could represent the approach of nap time.

Complicating matters further was the presence of numerous articles detailing adverse effects occurring with therapeutic doses, primarily representing the serotonin syndrome. Indeed, in some cases, these adverse effects were moderate to severe in nature (e.g., seizures, hyperthermia) and were often difficult to distinguish from the effects seen with overdoses.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

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

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Nelson LS, Erdman AR, Booze LL, Cobough DJ, Chyka PA, Woolf AD, Scharman EJ, Wax PM, Manoguerra AS, Christianson G, Caravati EM, Troutman WG. Selective

serotonin reuptake inhibitor poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 May;45(4):315-32. [107 references] [PubMed](#)

ADAPTATION

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

DATE RELEASED

2006 Oct 30

GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

SOURCE(S) OF FUNDING

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

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Erdman was an employee of AstraZeneca during his work on this guideline, and Dr. Booze's husband is employed by AstraZeneca.

There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

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

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

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on December 18, 2007. The information was verified by the guideline developer on January 14, 2008.

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