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

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PRACTICE GUIDELINE

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

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A review of US poison center data for 2004 showed over 48,000 exposures to selective serotonin reuptake inhibitors (SSRIs). A guideline that determines the conditions for emergency department referral and prehospital care could potentially optimize patient outcome, avoid unnecessary emergency department visits, reduce health care 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 out-of-hospital triage and initial management of patients with a suspected ingestion of an SSRI by 1) describing the process by which an ingestion of an SSRI might be managed, 2) identifying the key decision elements in managing cases of SSRI 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 immediate-release forms of SSRIs alone. Co-ingestion of additional substances might require different referral and management recommendations depending on their combined toxicities.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of 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) 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 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 patients already on an SSRI, those with 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°F [>40°C]) for SSRI-induced

serotonin syndrome. This should be done in consultation with and authorized by EMS medical direction, by a written treatment protocol or policy, or with direct medical oversight (Grade C).

Keywords   Serotonin uptake inhibitors/poisoning; Poison control centers/standards; Practice guidelines

Introduction

Scope of the problem and importance of this guideline

Antidepressant overdoses are among the most common prescription drug overdoses managed by poison centers. This is in part because of their high prevalence of therapeutic use but also because of their use by patients at high risk for intentional ingestion. According to the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers, there were 48,204 human ingestions of selective serotonin reuptake inhibitor antidepressants (SSRIs) reported to poison centers in the US in 2004; 31,181 (65%) were evaluated in healthcare facilities. Children less than 6 years of age accounted for 8,187 (17%) of all reported SSRI ingestions. Major effects occurred in 1,426 SSRI ingestions and 103 ingestions resulted in death; there were known co-ingestants in all but three deaths (1). Between 2000 and 2005, there were 44,545 ingestions of SSRIs in children less than 6 years of age reported to TESS. Major effects were noted in 59 cases (0.1%) and there was one reported death (2).

The evaluation and management of possible SSRI poisoning has medical, economic, and social costs. It is critical to decide on a strategy that could be used to determine which patients need referral to healthcare facilities for medical evaluation. Poison centers usually recommend emergency department evaluation of any patient who becomes severely symptomatic or intentionally ingests a substance to cause self-harm. The most important decision for the remainder of patients exposed to an SSRI (i.e., unintentional and asymptomatic or mildly symptomatic) is to determine who requires emergency department evaluation. Typical unintentional exposure scenarios include a child who is found handling an SSRI medication container and who might have ingested one or more tablets or an adult or child who already takes an SSRI and inadvertently doubles or triples their dose. Referring every patient with a potential or documented SSRI ingestion to an emergency department is unnecessarily expensive and labor intensive (3), since the therapeutic indices of the SSRIs are generally very favorable. However, drug interactions are common and can be serious.

Background

SSRIs represent a group of chemically diverse agents that share the ability to inhibit the presynaptic uptake of serotonin within the central nervous system. They are commonly prescribed for the initial treatment of mild to moderate depression, generalized anxiety disorder, and obsessive-compulsive disorder and are widely used for other diseases of neurologic origin including neuropathic pain (4–6). Due to their less troublesome side effect and safety profiles, the SSRIs have essentially replaced the tricyclic antidepressants as first-line therapy for depression. They are available only by prescription.

Six pure SSRIs are available in the US: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft); these agents are the subject of this guideline. The prolonged-release formulations of paroxetine (Paxil CR) and fluoxetine (Prozac weekly) are not directly considered by this guideline given their relatively recent release and the lack of available overdose/toxicity data. 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.

SSRIs are associated with several relatively common adverse effects. The most frequently noted are nausea, vomiting, and diarrhea (6,7). Insomnia, anxiety, and hypomania are common psychological effects and are most typical after chronic dosing.

Symptoms observed following overdose of an SSRI are typically mild and manifest primarily as central nervous system depression (6,7). Seizures and cardiac electrophysiologic abnormalities (generally QTc interval prolongation) can occur and are most widely reported following overdoses with citalopram (8–11). Consequential clinical effects can result uncommonly from any agent of this class due to the development of the serotonin syndrome, which manifests as autonomic instability, altered mental status, seizures, extrapyramidal syndrome including muscle rigidity, hyperthermia, and, rarely, death. However, nearly all reported cases involve patients using multiple serotonergic agents (e.g., tricyclic antidepressant, lithium, meperidine) or who have large exposures to a single serotonergic agent. The onset and progression of clinical toxicity, including the serotonin syndrome, is generally gradual over several hours, although after large overdose or with certain drug interactions it can be abrupt (12).

The FDA has issued a warning on the use of paroxetine during pregnancy due to the risk of adverse fetal outcomes such as an increased risk of congenital malformations, particularly cardiac (13). Whether this is a class effect or a concern following short-term or one-time exposure, early or late in pregnancy, remains to be determined. Regardless, SSRIs are still utilized for pregnant and lactating women, despite warnings in labels against such use and the categorization of SSRIs as FDA Pregnancy Category C or D (14,15).

Definition of terms

For the purposes of this analysis, age groups are defined as 1) children less than 6 years of age and 2) children 6 years of age or older and adults. The older age group is much more likely to attempt self-harm and to conceal an ingestion. The terms "out-of-hospital" or "prehospital" are defined as the period before a patient reaches a healthcare facility. An acute ingestion is defined as any number of ingestions that occur within a period of 8 hours. The following definitions for clinical effects are used throughout the guideline and are adapted from those used by TESS. The descriptor "mild" means that the clinical effects were generally limited to vomiting, somnolence (lightly sedated and arousable with speaking voice or light touch), mydriasis, or diaphoresis. The term "moderate" includes vital sign abnormalities, particularly mild hyperthermia, agitation, or lethargy (sedated but arousable with more than speaking voice or with irritating stimuli). "Severe" includes clinically significant vital sign or cardiovascular abnormalities, particularly those that require intervention such as life-threatening hyperthermia, agitated delirium, coma (requiring painful stimuli to arouse or unarousable), or seizures (see TESS for more complete definitions). The severity of the serotonin syndrome can be similarly qualified (12).

Intended users of the guideline

The intended users of this guideline are personnel in US poison centers. This guideline has been developed for the conditions prevalent in the US. While the toxicities of the 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.

Objective of the guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with a suspected ingestion of an SSRI by 1) describing the process by which an ingestion of an SSRI might be managed, 2) identifying the key decision elements in managing cases of SSRI 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 immediate-release forms of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline alone. 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.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of 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 (16,17). 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 US poison center experience, and be an opinion leader with broad esteem. Two specialists in poison information were included as full panel members to provide the viewpoint of the end-users of the guideline.

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 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 poisoning managements 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 Toxicology 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).

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 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. Attempts were 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 AAPCC website.

Criteria used to evaluate studies and assign levels of evidence

The articles were assigned level-of-evidence scores based on the Grades of Recommendation table 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.

Guideline writing and review

A guideline draft was prepared by the lead author (listed first). The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, 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. 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 website 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.

Review of current practices

Current poison control center practices

To gather information for this guideline, a message was sent in 2004 to all US poison centers requesting the triage guidelines that they were utilizing for managing patients with SSRI poisonings. Sixteen poison centers responded. One center submitted a triage guideline. According to the submitted guideline, children under 5 years of age could be observed at home following paroxetine ingestions of up to 180 mg; details on the disposition of patients exposed to the other SSRIs were not included. Fifteen poison centers indicated that they did not have triage guidelines for SSRI ingestion. The reasons why these centers did not have triage guidelines are unknown, but this supports the need for the development of this guideline.

Dose

The evaluation of dose in the out-of-hospital environment is limited to an estimation based on the patient's history and the

assessment of the product and its packaging (when available for evaluation). The estimated dose of each SSRI for an acute ingestion is determined by multiplying the number of units thought to have been ingested by the amount of drug contained in each unit. If precise data for an ingestion are unknown or unclear (package size, unit size, number of units ingested), poison centers in the US typically utilize a method in which the maximum potential dose is calculated. For example, if the actual dose ingested cannot be determined, the number of the SSRI dosage units that are missing can be multiplied by the dose of the individual tablet. When the mg/kg dose or a child's weight was not included in an article, the mg/kg dose was estimated by the use of pediatric growth charts (18). The 95th percentile weight was used for a particular age and sex. When the sex of the child was not stated, the weight for boys was used. This approach errs on the side of estimating a lower mg/kg dose. Estimated mg/kg doses are italicized throughout the guideline whenever they are presented.

Time since ingestion

Ascertaining the time since ingestion is useful in evaluating the potential for toxicity and determining the need for healthcare facility referral and the duration of observation there. Once the time of peak effect has passed, an asymptomatic patient with an unintentional ingestion might not require referral to a healthcare facility just because the dose exceeded a critical threshold.

Evaluation of evidence

When reviewing the textbooks and published literature, qualitative clinical descriptors are frequently included. In other cases, for brevity of this guideline, detailed clinical descriptors are converted to qualitative terminology (see Definition of Terms, above).

Review of poisindex

Poisindex, a computerized toxicology reference used by poison control centers, states that children 6 years of age or younger with ingestions of fluoxetine less than 60 mg or 5 mg/kg can be monitored at home. There are no specific statements regarding the other SSRIs (4).

Review of the AAPCC TESS fatality abstracts

A review of the fatality data for the period of 2000–2005 identified two SSRI-related deaths that were not suicidal or questionable in intent and did not involve co-ingestants. The youngest reported death in which an SSRI was listed as the only substance was that of a 3-year-old boy given "2 sertraline capsules to calm him down." The child was found face down in a creek and the postmortem examination was consistent with drowning. A 16-year-old with a history of syncope suffered sudden cardiac death; there was no mention of SSRI use or overdose in this report. There were also three deaths that were consistent with the serotonin syndrome.

Review of textbooks

A review of SSRI poisoning chapters in five toxicology textbooks revealed variation in their recommendations. One book noted that newer antidepressants, which include the SSRIs, "generally have a wide therapeutic index, with doses in excess of 10 times the usual therapeutic dose tolerated without serious toxicity" (19). One textbook did not provide triage guidelines but stated "…because of the wide therapeutic index of the SSRIs, most patients will have mild or no symptoms after an overdose" (20). Another made neither global nor specific triage recommendations (21). Another chapter said that "patients with well-defined small unintentional ingestions may be managed at home with close observation," although "small" is not defined (6). The final book stated that "…moderate overdoses (up to 30 times the usual daily dose) are associated with minor symptoms…" although specific decision-making recommendations regarding emergency department evaluation were not provided (22).

The therapeutic dosing regimens for adults described in the individual SSRI prescribing information are displayed in Table 1. Since research on the use of the SSRIs in children is ongoing, dosing for children is not included in the prescribing information. The therapeutic dosing for children listed in three drug and pediatric reference textbooks is presented in Table 1 (5,23,24).

Acute ingestions in patients less than 6 years of age

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are not FDA-approved for use in this age group. These drugs might be used by some clinicians, but their use is controversial given the possible association with suicidal thinking or behavior (suicidality) especially during the first few months of treatment (25). It is unknown whether suicidality would develop from an acute ingestion, but this seems unlikely. A minimal toxic dose for these drugs in children is not cited in Poisindex except as noted above for fluoxetine (4). There were no articles identified in which single doses of any SSRI were intentionally given to patients less than 6 years of age and associated with subsequent toxicity.

Citalopram

There were no level 1–3 articles with dose-toxicity information. However, there were three level 4 or 6 articles that included patients less than 6 years of age with acute citalopram ingestions and from which some dose-toxicity information could be extracted (9,26,27). Unfortunately, most of

Table 1. Summary of therapeutic dosing for SSRIs

Drug	Starting daily therapeutic dose	Maximum daily therapeutic dose	Dosage forms
Citalopram	Adult: 20 mg	60 mg	10, 20, 40 mg tablets 10 mg/5 mL oral solution
	Child: not available	Not available	
Escitalopram	Adult: 10 mg	20 mg	5 mg, 10 mg, 20 mg, tablets 5 mg/5 mL oral solution
	Child: not available	Not available	
Fluoxetine	Adult: 20 mg	80 mg	10, 20, 40 capsules 10 mg tablets 90 mg weekly capsules 20 mg/5 mL oral solution
	Child (6–18 yr): 10 mg	20 mg	
Fluvoxamine	Adult: 50 mg	300 mg	25, 50, 100 mg tablets
	Child (8–17 yr): 25 mg	200 mg	
	Child (<8 yr): not available	Not available	
Paroxetine	Adult: 20 mg	60 mg	10, 20, 30, 40 mg tablets 10 mg/5 mL oral suspension *Paxil CR controlled-release tablets* 12.5, 25, 37.5 mg
	Child: 10 mg	60 mg	
Sertraline	Adult: 50 mg once daily	200 mg	25. 50. 100 mg tablets 20 mg/mL oral concentrate
	Child (6–12 yr): 25 mg once daily	200 mg	
	Child (<6 yr): not available	Not available	

these articles reported the ages and doses as ranges or using summary data, making it impossible to associate clinical effects with dose and age. Since several of the articles did not specify patient ages, or included patients 6 years of age and older, it was impossible to know which doses referred to patients of what age. With these issues in mind, an abstract of a retrospective review of 228 citalopram ingestions in patients of all ages (level 6) reported doses ranging from 40 to 5000 mg, some of which resulted in toxic effects ranging from mild to severe (9). An abstract (level 6) of a prospective observational study of 42 cases (all ages) of citalopram ingestion in which doses ranged from 100 to 2400 mg (2–34.5 mg/kg) noted that the resulting clinical effects ranged from none to severe (27).

Escitalopram

There were no level 1–4 articles with dose-toxicity information. There was a single level 6 abstract of a retrospective review of 33 patients (of all ages) with acute escitalopram ingestions. Doses ranged from 30 to 1400 mg, and some of these patients went on to develop effects ranging from mild to severe (9).

Fluoxetine

There were no level 1–3 articles with dose-toxicity information. However, there were three level 4 case series that included patients less than 6 years of age with acute fluoxetine ingestions and from which some dose-toxicity information could be extracted (28–30). The first article was a retrospective review of fluoxetine ingestions by 120 patients

less than 6 years of age in which doses ranged from 10 to 400 mg. Only four of these patients developed adverse effects, all mild (three had vomiting, one had sedation), and the patient with the lowest dose (20 mg) had sedation (details about the patients' ages and weights were not reported) (28). A retrospective review of 37 acute ingestions reported doses of 20–600 mg as being associated with clinical effects ranging from no symptoms to symptoms of moderate severity (details about the patients' ages and weights were not reported) (30). Finally, in a retrospective review of data reported to the FDA and TESS, fluoxetine ingestions as low as 100 mg were reported to be associated with seizures, and ingestions of as little as 260 mg were reported to be associated with death; however, direct causality by fluoxetine could not be assessed in these cases (details about the patients' ages and weights were not reported) (29). There was also a single level 4 case report in which an ingestion of up to 700 mg (*43 mg/kg*) by a 4-year-old girl resulted in sequelae including agitation, dyskinesia, and a transient period of unconsciousness within 3 hours of ingestion from which she recovered by the time she arrived at an emergency department 1 hour later. She had a significantly elevated admission serum fluoxetine concentration that remained elevated when repeated at 40 hours after admission (31).

Fluvoxamine

There were no level 1–3 articles with dose-toxicity information. However, there were two level 4 case series that included patients less than 6 years of age with acute fluvoxamine ingestions and from which some dose-toxicity information

could be extracted. In a review of 78 patients of all ages with acute fluvoxamine ingestions, the lowest dose associated with any toxicity was 150 mg (age unknown; abdominal pain, drowsiness), while the lowest dose associated with severe toxicity (bradycardia and prolonged prothrombin time) was 600 mg in a 2-year-old child (*40 mg/kg*). The lowest dose associated with death was 2500 mg, but the age was unreported (co-ingestants could have been involved in some cases) (32). There was also a single level 4 case report in which a 4-year-old boy developed hypotension, bradycardia, and seizure after an unverified ingestion of 400 mg (*20 mg/kg*) (33).

Paroxetine

There were no level 1–3 articles with dose-toxicity information for paroxetine. However, there were four level 4 or 6 case series of patients less than 6 years of age with acute paroxetine ingestions from which some dose-toxicity information could be extracted. In two papers that appeared to have overlapping patient sets, the lowest dose of paroxetine associated with any toxicity was 30 mg, which resulted in mild effects (i.e., drowsiness) (34,35). An abstract (level 6) described 149 cases of paroxetine ingestion by children less than 6 years of age with doses ranging from 20 to 240 mg. Twelve children developed mild effects, but their specific doses were not reported (36). In a retrospective review of data reported to the FDA and TESS (level 4), paroxetine ingestions as low as 530–600 mg were reported to be associated with death; however, direct causality could not be assessed in these cases (details about the patients' ages and weights were not reported) (29).

Sertraline

There was a single level 3b article that combined 2 years of retrospective record review with 6 months of prospective data collection for sertraline. In this paper, which included patients of all ages reported together, the lowest dose of sertraline associated with any effects was 200 mg (37). In addition, there were three level 4 or 6 case series that included patients less than 6 years of age with acute sertraline ingestions and from which some dose-toxicity information could be extracted. An abstract described 14 sertraline ingestions by children 5 years of age and younger; doses, when known, ranged from 12.5 to 250 mg and were associated with minor effects in only one patient; the exact dose for this patient was not reported (38). In a retrospective review of 40 sertraline overdose patients aged 1–69 years (level 4), the range of doses was 50–8000 mg and these were associated with effects ranging from none to severe (39). In a retrospective review of data reported to the FDA and TESS (level 4), sertraline ingestions of 500–1000 mg were associated with seizures and/or ECG abnormalities, and an ingestion of 1100 mg was associated with death; however, direct causality could not be assessed in these cases (29). There were also two level 4 case reports. In the first, a 22-month-old girl developed minor effects after ingesting 250–300 mg of sertraline (40). In the

second, a 5-year-old girl developed severe effects consistent with the serotonin syndrome, including hyperthermia to 39.1°C (102.4°F), after an ingestion of more than 400 mg (41).

Acute ingestions in patients 6 years of age and older

Other than for paroxetine and sertraline described below, there were no articles reviewed in which single doses of an SSRI (i.e., citalopram, escitalopram, fluoxetine, fluvoxamine) were given to patients 6 years of age and older and associated with subsequent toxicity.

Citalopram

There were no level 1–3 articles with dose-toxicity information. However, there were several level 4 or 6 articles that included patients 6 years of age and older with acute citalopram ingestion and from which some dose-toxicity information could be extracted (8,9,11,26,27,42,43). Unfortunately, most of these articles reported the ages and doses as ranges or using summary data, making it impossible to associate clinical effects with dose and age. Since several of the articles did not specify ages or included patients less than 6 years of age, it was impossible to know which doses referred to patients of what age. An abstract (level 6) of a retrospective review of 228 citalopram ingestions in patients of all ages reported doses ranging from 40 to 5000 mg and toxic effects ranging from mild to severe. Although the outcomes appeared to be excellent (there was one major and 20 moderate outcomes), the abstract reported that 17 of 228 patients (of all ages and all doses) developed seizures (9). An abstract (level 6) of a prospective observational study of 42 cases (all ages) of citalopram ingestion in which doses ranged from 100 to 2400 mg (2–34.5 mg/kg) described effects ranging from none to severe (27). Two articles by the same authors (level 4) reported that ingestions less than 600 mg resulted only in mild effects, while doses greater than 600 mg frequently resulted in moderate effects 18–33% of the time and doses greater than 1700 mg often caused severe toxicity (42,43). Another article (level 4) reported the development of seizures in four patients after ingestions of an estimated 400–5200 mg (8). One case series (level 4) of antidepressant overdoses included 88 patients with a mean age of approximately 33 years (likely all adults). Seizures occurred in five patients following doses of 400–3000 mg. The mean QTc for the group of 88 patients was not significantly prolonged compared to the patients who overdosed on other antidepressants, although the range of QTc durations was not provided and comparison was not made with the patients' baseline QTc durations. Seven patients developed QTc durations longer than 450 msec, but no dysrhythmias were noted (10). An additional paper reported deaths associated with ingestions as low as about 840 mg. However, the dose estimates were made postmortem, and other co-ingestants might have contributed to the patients' deaths (11).

There were several level 4 or 6 articles with individual case information presented in detail. Specifically, there were

12 cases reported in 11 articles (42–52). Among them, the lowest dose of citalopram associated with any toxicity was 400 mg, which was reported to be associated with severe toxicity in at least two adults (42,47).

Escitalopram

There were no level 1–4 articles with dose-toxicity information. However, there were two level 6 abstracts that included multiple patients 6 years of age and older with acute escitalopram ingestions and from which some dose-toxicity information could be extracted. The first abstract was a retrospective review of 33 patients of all ages with acute escitalopram ingestions. Doses ranged from 30 to 1400 mg, and some of the patients went on to develop effects ranging from mild to severe (9). The second abstract was a retrospective review of 14 patients, aged 14–44 years, with doses ranging from 100 to 600 mg; seven patients developed effects ranging from mild to moderate (53). There was also an abstract of a single case report (level 6) reporting ingestion of 100–200 mg by a 38-year-old man resulted in severe toxicity (54).

Fluoxetine

There were no level 1–3 articles with dose-toxicity information. However, there were four level 4 case series that included patients 6 years of age and older with acute fluoxetine ingestions and from which some dose-toxicity information could be extracted (29,30,55,56). Unfortunately, most of these articles reported the ages and doses as ranges or using summary data, making it impossible to associate clinical effects with dose and age. Since several of the articles did not specify ages or included patients less than 6 years of age, it was impossible to know which doses referred to patients of what age. One retrospective review of 37 acute ingestions reported doses of 20–600 mg as being associated with effects ranging from no symptoms at all to symptoms of moderate severity (30). In a retrospective review of data reported to the FDA and TESS, fluoxetine ingestions as low as 100 mg were reported to be associated with seizures and ingestions of as little as 260 mg were reported to be associated with death; however, direct causality by fluoxetine could not be assessed in these cases (29). There were also 11 level 4 or 6 articles with individual case information on acute fluoxetine ingestions in patients 6 years of age and older (57–67). Among them, the lowest dose of fluoxetine associated with any toxicity was 80 mg in a 32-year-old woman who developed severe effects but had also ingested other drugs (level 6) (64). The self-reported ingestion of 680 mg by a 19-year-old woman (level 4) resulted in a flu-like syndrome of unclear relation to the overdose (62).

Fluvoxamine

There were no level 1–3 articles with dose-toxicity information. However, there were three level 4 case series that included patients 6 years of age and older with acute fluvoxamine

ingestions from which some dose-toxicity information could be extracted (32,68,69). In one, specific doses were not given but, according to the authors, ingestions of up to 2000 mg were associated with mild effects (69). In another article, a combination of two retrospective reviews of acute fluvoxamine ingestions (221 and 78 patients), the lowest dose associated with any toxicity was 150 mg (abdominal pain, drowsiness, tremor), while the lowest dose associated with severe toxicity in an adult was 750 mg (bundle branch block). The lowest dose associated with death was 2500 mg, but the patient's age was not reported (co-ingestants might have been involved in some cases) (32). There were nine level 4 or 6 articles with individual case information on acute fluvoxamine ingestions in patients 6 years of age and older (70–78). In one report, an 11-year-old boy developed severe toxicity after a single dose of 50 mg but he was also on perphenazine and benztropine chronically (74). The next lowest dose of fluvoxamine associated with toxicity was 1500 mg in a 31-year-old woman who developed severe effects but had a coingestion of thiocolchicoside, which itself has been associated with seizures (78,79). The lowest reported ingestion associated with death was 4200 mg (72).

Paroxetine

There were two articles reviewed in which single doses of paroxetine were given to adults and associated with subsequent adverse effects; one was a level 1b study (80), and the other was a level 2b (81). Between these trials, paroxetine doses of 50–60 mg in adult volunteers resulted in mild effects.

There were no level 3 articles with dose-toxicity information for paroxetine. However, there were three level 4 or 6 retrospective reviews that included patients 6 years of age and older with acute paroxetine ingestion and from which some dose-toxicity information could be extracted. In two papers that appeared to have overlapping patient sets, the lowest dose of paroxetine associated with any toxicity was 10 mg in patients with co-ingestants and 200–400 mg in patients without co-ingestants. The clinical findings in this group were mild and consisted of vomiting, mydriasis, drowsiness, and tachycardia (34,35). In a retrospective review of data reported to the FDA and TESS, paroxetine ingestions as low as 530–600 mg were reported to be associated with death; however, direct causality could not be assessed in these cases (29). One paper (level 4) provided additional detail about 15 patients with paroxetine overdose, five of whom were hospitalized and recovered (12). There were also a number of level 4 or 6 articles with individual case information on acute paroxetine ingestions in patients 6 years of age and older. Specifically, there were 12 cases reported in 11 articles (59,73,82–90). Among them, the lowest dose of paroxetine associated with any adverse effect was 20 mg in two patients who developed moderate sequelae but who were both chronically taking other serotonergically active agents (59,90). The lowest dose associated with severe toxicity was 360 mg (82).

Sertraline

Sertraline is approved for use in children and adolescents for the treatment of obsessive compulsive disorder at dosages of 25 mg once daily for ages 6–12 years and 50 mg once daily for ages 13–17 years. The typical dosage of sertraline in adults is 50 mg once daily.

In a randomized crossover study (level 1b), single doses of sertraline were given to adults (50–67 years of age) who then underwent psychomotor function testing. Single doses of 100 mg were associated with mild effects (e.g., drowsiness) within 4 hours, although they raised the systolic blood pressures of subjects by a mean of 12 mm Hg, which could be considered a moderate effect (91).

A level 3b article combined retrospective and prospective dose-toxicity data for sertraline. In this paper, which included patients of all ages reported together, the lowest dose of sertraline associated with any effects was 200 mg (37). While the collection of data in this report was prospective, the estimation of dose was retrospective and, thus, subject to inaccuracy. In addition, there were a few level 4 or 6 retrospective reviews that included patients 6 years of age and older with acute sertraline ingestions and from which some dose-toxicity information could be extracted. In a retrospective review of 40 sertraline overdoses (of all ages), the range of doses was 50–8000 mg, and these were associated with effects ranging from none to severe (39). An abstract (level 6) of a retrospective review of sertraline ingestions in 47 children 5 years of age and older reported that doses, when known, ranging from 100 to 4500 mg were associated with minor effects in 22 patients (28). In a retrospective review of data reported to the FDA and TESS, ingestion of 500–1000 mg were associated with seizures and/or ECG abnormalities, and an ingestion of 1100 mg was associated with death; however, direct causality could not be assessed in these cases (29). There were also a number of level 4 or 6 articles with individual case information on acute sertraline ingestions in patients 6 years of age and older. Specifically, there were 10 cases reported in nine articles (59,92–99). Among them, the lowest dose of sertraline associated with any toxicity was 750 mg ingested by a 42-year-old who had also ingested moclobemide, which resulted in moderate toxicity (59). The lowest dose associated with severe toxicity was 4000 mg in a 14-year-old girl who had also ingested naproxen sodium (97).

Onset of effects

The panel members expressed interest in taking into account the time of onset for toxicity to develop after SSRI ingestions in order to help make decisions about out-of-hospital transportation and management. Therefore, all articles with toxicity were searched for evidence documenting or estimating times of onset. Unfortunately, the vast majority of articles reported times of presentation to healthcare facilities but not times of symptom onset, which probably occurred earlier. Thus, in most cases, it was only possible to establish an upper limit of time to onset. In only a few reports was an exact time of onset known and reported. For this reason, a separate time of onset table was not constructed. Although it is unknown whether the time to peak serum concentration is a suitable marker for predicting toxicity, this time for each of the SSRIs discussed in this review is generally 8 hours or less.

There were too few data to separate time of onset by patient age. Similarly, there were neither enough data nor any apparent difference in onset of effects between individual SSRI agents. Therefore, this summary makes no effort to divide the data by individual agent or different patient age groups.

In discussing the onset of effects after SSRI ingestion, care should be taken to distinguish the initial onset of effects from the onset of serious or major effects, time to peak effects, or time to delayed effects or later deterioration. Furthermore, decontamination measures might have differed between articles. Additionally, in essentially all of these studies, it was not clear whether, or what, symptoms were present before the late-occurring event.

In most cases, the time of onset of initial effects after SSRI ingestion, when reported, was within a few hours (Table 2). There was only one case reviewed that indicated the occurrence of significant clinical effects more than 4 hours after SSRI ingestion, due potentially to a drug interaction, in the absence of any prior signs or symptoms. This was an abstract (level 6) of a case report of an elderly woman on St. John's wort who developed serotonin syndrome 8 hours after a single dose of paroxetine (90). There was a level 3b combined retrospective and prospective report of 52 sertraline ingestions in which the onset of effects was reported as occurring within ½–10 hours of ingestion (37). There were published cases in which significant toxic effects (e.g., serotonin syndrome, cardiac toxicity, or seizures) occurred 4–24 or more hours after ingestion, but in all such cases at least some signs or symptoms (albeit mild in some cases) were present earlier in the patient's course (37,39,47,51,56,57,61,90,97). In a retrospective review of 44 cases of citalopram ingestion, seizures were noted to occur "within the first few hours" while ECG effects like QRS or QTc changes, were noted "later" (43). There was an abstract (level 6) that described a 42-year-old man who had ingested paroxetine along with haloperidol and developed polymorphic ventricular tachycardia 31 hours later (85). However, it was felt that the paroxetine was not the cause of the effects in this case but that its presence delayed the metabolism of haloperidol, resulting in delayed haloperidol toxicity. There was a case of flu-like or allergic findings (rash, myalgia, headache) developing around 2 days after an acute ingestion of fluvoxamine (62).

The rapidity of effect onset after SSRI ingestion was variable. In most cases, effects came on or progressed relatively slowly over the course of minutes to hours. However, there was a report of severe effects developing suddenly and/or without warning after citalopram overdose, although the timing relative to the ingestion time was not reported (52). A few patients who developed clinical effects from SSRI poisoning

Table 2. Details of dose and time to onset associated with more than mild toxicity following acute SSRI overdose*

Drug	Time to peak serum concentration[†]	Lowest reported acute dose to produce more than mild toxicity	Longest reported delay in onset of toxicity after acute overdose
Citalopram	4 hr	Adult: 400 mg	<13 hr
		Child: NA	NA
Escitalopram	5 hr	Adult: 100 mg	NA
		Child: 100 mg	NA
Fluoxetine	6–8 hr	Adult: NA	NA
		Child: 100 mg	NA
Fluvoxamine	3.8 hr	Adult: 750 mg	NA
		Child: 400 mg	NA
Paroxetine	4.9–6.4 hr	Adult: 360 mg	6 hr
		Child: NA	NA
Sertraline	4.5–8.4 hr	Adult: 500 mg	3 hr
		Child: 400 mg	4 hr

*The table reflects cases that excluded co-ingestants and in which reasonable validation was present. Development of serotonin syndrome resulting from a drug interaction is also excluded.

[†]Derived from prescribing information for the individual drugs.

went on to worsen to varying degrees over the course of hours to days. Usually, the deterioration was progressive but not catastrophic. In the majority of the cases there were coingestants and the relative role of each was undetermined (37,43,51,57,61,86,92,97).

Serotonin syndrome

Serotonin syndrome is a clinical syndrome that manifests as autonomic instability, altered mental status, seizures, extrapyramidal syndrome including muscle rigidity, hyperthermia, and, rarely, death. The onset of serotonin syndrome is usually within 6 hours of ingestion with an escalating severity of clinical abnormalities. Serotonin syndrome appears to be due, in large part, to excessive stimulation of the 5-HT[2A] subtype of the central nervous system serotonin receptors. Although serotonin syndrome could occur following isolated ingestion of a serotonergic agent, including a therapeutic dose, serotonin syndrome occurs more commonly in patients with chronic ingestion of an SSRI. Drug interactions are also commonly implicated in serotonin syndrome. Although not exclusively related to interactions with SSRIs, drugs that can interact with SSRIs to cause serotonin syndrome include monoamine oxidase inhibitors, meperidine, dextromethorphan, lithium, clonazepam, methylenedioxymethamphetamine (MDMA, Ecstasy), and the dietary supplements tryptophan and St. John's wort (12).

Potential out-of-hospital treatments

Gastrointestinal decontamination

There were a number of different decontamination measures reported in the reviewed literature, including activated charcoal,

ipecac syrup, gastric lavage, and various cathartics. Most of these measures had too little evidence to comment on their efficacy, and others are not likely to be available in an out-of-hospital setting. Only those decontamination measures that could reasonably be expected to be available and carried out in an out-of-hospital setting and which had a significant amount of data are reviewed in this summary. These are activated charcoal and ipecac syrup.

Activated charcoal

There were no prospective trials reviewed that investigated the efficacy of activated charcoal on SSRI absorption after overdose. There were also no articles reviewed with controlled data (e.g., case-control or cohort studies) on activated charcoal efficacy after SSRI overdose. There were numerous level 4 or 6 case reports, case series, or abstracts in which single or multiple doses of activated charcoal were given to patients with SSRI overdose, 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, and the fact that activated charcoal does not produce immediate clinical improvement (i.e., outcomes were generally measured by improved kinetic parameters or the prevention of later clinical sequelae).

There were three prospective clinical trials (all level 1b) on the efficacy of activated charcoal at binding various SSRIs but these were all volunteer studies employing therapeutic SSRI doses (one study each for paroxetine, fluoxetine, and citalopram) and activated charcoal was administered shortly after ingestion of the SSRI, so their applicability to the overdose situation remains unclear. In all three studies, oral activated charcoal substantially reduced SSRI absorption compared to the control phase as measured by serial pharmacokinetic measurements (80,100,101). Since altered mental status (drowsiness) is a frequent complication of SSRI overdose,

the potential risk for aspiration of orally administered activated charcoal should be considered (102).

Ipecac-induced emesis

There were no controlled trials of ipecac syrup for SSRI overdose. Nor were there any prospective volunteer studies examining the efficacy of ipecac in reducing SSRI absorption, even after therapeutic doses. There were multiple case reports and case series (level 4) in which ipecac syrup was administered after SSRI overdose (37,68,103). In none of these reports was the description of the circumstances surrounding the use of ipecac syrup detailed sufficiently to draw conclusions concerning its efficacy or safety. Since altered mental status (drowsiness) is a frequent complication of SSRI overdose, the potential risk for aspiration following ipecac-induced emesis should be considered.

Other treatment measures

Several different treatment measures were reported in the reviewed literature on SSRI toxicity/overdose. Most of the treatments had too little evidence available to comment on their efficacy. Indeed, there were no prospective or even retrospective controlled data (either in the out-of-hospital or in-hospital setting) for any of the treatment measures. Therefore, only those measures that anecdotally appeared to give temporal improvement, based on individual case reports or case series (level 4 or 6), and that might reasonably be available in the out-of-hospital setting are mentioned here.

Sodium bicarbonate

Sodium bicarbonate was used in several case reports. In two cases, intravenous sodium bicarbonate was temporally associated with QRS narrowing in patients with cardiac conduction abnormalities after SSRI poisoning—one citalopram and one fluoxetine (47,59). An 82-year-old woman who intentionally ingested citalopram 1.6 g developed a junctional bradycardia that reportedly responded to sodium bicarbonate (level 4). However, the link between citalopram and this dysrhythmia is tenuous (104). In an abstract (level 6), it was used along with multiple other measures in the initial resuscitation of a patient in cardiac arrest (52). In the final case (level 4), it might have been associated with improvement in CNS effects such as seizures, but the patient had also received other treatments (67). In many cases, the possibility of tricyclic antidepressant poisoning was not completely evaluated.

Supportive and symptomatic treatment

There were a number of general supportive measures reported in the SSRI overdose literature including oxygen, intubation and ventilation, CPR, IV fluids, benzodiazepines, anticonvulsants, pressors, antidysrhythmics, dextrose, cooling, treatment of allergic reactions, and antibiotics.

Since none of these has controlled data to support its efficacy in SSRI toxicity, the anecdotal reports are not presented here.

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 (105). 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.

Conclusions

Key decision points for triage

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 who has an SSRI. These variables include the patient's intent, the patient's symptoms, the product and the dose ingested, the time since the ingestion, and co-ingestants. The expert consensus panel agreed that in each case, the judgment of the specialist in poison information, the poison center medical director, or other poison center-affiliated clinicians might override any specific recommendation from this guideline.

Patient intent

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

Patient symptoms

There were a number of articles reporting adverse effects occurring with therapeutic SSRI dosages, mostly mild to moderate in nature. Furthermore, it is likely that there are many other such articles that were not identified or recovered and, therefore, not reviewed for this guideline because of the search criteria used to identify articles. In the absence of an established toxic dose, the expert consensus panel concluded that the presence of more than mild clinical effects (mild effects include vomiting, somnolence [lightly sedated and arousable with speaking voice or light touch], mydriasis, or diaphoresis), including those consistent with serotonin syndrome, should be used as an indication for emergency department referral regardless of the dose reportedly ingested. Patients who have unintentional SSRI ingestions and are asymptomatic could stay at home with poison center follow-up.

Dose

There is little information in the literature to adequately define a minimum acute toxic dose of any SSRI. Several reviews that included summary data concluded that the SSRIs as a class have a wide margin of safety, particularly when compared to the tricyclic antidepressants and monoamine oxidase inhibitors (26,29,106). Since none of these medications are approved for use in children less than 6 years of age and, therefore, do not have readily available dosing information in children, a triage determination based on a dose relative to a pediatric therapeutic dose is not possible. The panel concluded that for patients of all ages who use SSRIs therapeutically

and are asymptomatic or have only mild effects, doses greater than five times their personal single therapeutic dose (not daily dose) merit emergency department referral. For patients of all ages naïve to SSRIs who are asymptomatic or have only mild effects without concerning abnormal clinical findings, doses greater than five times the lowest adult initial therapeutic dose of any SSRI merit emergency department referral (i.e., citalopram 100 mg, escitalopram 50 mg, fluoxetine 100 mg, fluvoxamine 250 mg, paroxetine 100 mg, sertraline 250 mg). These doses for children are based on the fact that for the SSRIs that are indicated for use in older children and that there is overlap in the therapeutic dose ranges of children and adults, suggesting at least that an adult therapeutic dose is safe. The multiplicative factor is based on the generally accepted safety of the SSRIs even in patients with large overdoses. The extrapolation to the other SSRIs is made on the basis of their similar, class-based, toxicological profiles. This triage dose threshold is an attempt to balance the concern for adverse clinical effects with the desire to prevent the cost, risk, and intangible effects of an unneeded emergency department visit. Since the onset of clinical effect is generally gradual in those ingesting less than referral doses, waiting for the development of more than mild symptoms to prompt a visit to an emergency department should be safe.

Citalopram is regarded as the SSRI with the greatest potential for causing toxicity. There are reports of adverse electrocardiographic effects after non-massive overdose (107), which could be delayed in onset (51), although there is little specific dose or onset data on which to base clinical decisions (9,27). Based on the findings in the literature review there is no imperative at this time to alter the triage criteria for citalopram.

Time to onset of toxicity

There is little information in the literature to adequately define a minimum or a maximum time of onset of toxicity for any specific SSRI for patients less than 6 years of age. Based on the generally accepted safety of the SSRIs, the expert consensus panel concluded that patients who have unintentional 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) or up to five times their own dose if already on the SSRI and are asymptomatic or have mild effects (defined above) could stay at home with poison center follow-up since the likelihood of delayed toxicity is small as long as they remain asymptomatic. Since it is expected that the onset of toxicity should occur by the time peak serum concentrations are reached, observation for 8 hours is recommended based on the pharmacokinetics of the individual SSRIs. Consideration should be given to the time of day that home observation will take place, since observation during normal sleep hours might not be practical or reliable.

Potential out-of-hospital treatments

The expert consensus panel concluded that out-of hospital gastrointestinal decontamination offered potential benefit, but the risks and likely benefit to the patient were difficult to determine. Inducing emesis with ipecac syrup was concluded to carry the risk of pulmonary aspiration of gastric contents if the patient became sedated and is not supported by sufficient evidence of benefit to warrant its use. Moreover, ipecac syrup would likely delay or prevent the adminstration of activated charcoal, a potentially more effective treatment, and it might induce a vagal stimulus that could further depress heart rate. Activated charcoal was determined to be a useful treatment that could be administered orally in the prehospital setting, although the effectiveness and risks of activated charcoal have not been evaluated in the prehospital management of SSRI poisoning. Also, the panel agreed that transportation to an emergency department should not be delayed in order to attempt charcoal administration.

Serotonin syndrome

The primary adverse clinical effect associated with chronic ingestion of SSRIs is serotonin syndrome. There is no adequate support from the literature on which to base triage decisions. Since many consider the serotonin syndrome to be more likely to develop in patients on multiple serotonergic drugs, it seems prudent, although not strictly evidence-based, to closely observe for symptoms, either at home or in a hospital, any patient exposed to an SSRI who is taking a serotonergic agent (e.g., tricyclic antidepressant, monoamine oxidase inhibitor, dextromethorphan, lithium). Note that serotonin syndrome has been documented with therapeutic doses of SSRIs.

Recommendations

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 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 patients already on an SSRI, those with 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°F [>40°C]) for SSRI-induced serotonin syndrome. This should be done in consultation with and authorized by EMS medical direction, by a written treatment protocol or policy, or with direct medical oversight (Grade C).

These recommendations are summarized in Appendix 4.

Implications for research

The panel identified the following areas as needing additional research:

1. The acute toxic dose of each SSRI for different patient populations needs to be determined.
2. The maximal time to the onset of adverse clinical effects for each SSRI remains unclear and could be determined by case investigation. Verification of ingestion, exclusion of alternative explanations, and detailed corroborative history would be required of such case reports.
3. The prevalence, minimal responsible dose, time to onset, and consequences of the effects of citalopram on cardiac electrophysiology (as measured both by the electrocardiogram and clinically) need clarification. This could be done through clinical trials or, more likely, by enhanced reporting in case reports or case series.
4. Risk factors for the development of the serotonin syndrome are not known other than in generalities such as "massive overdose" or "combinations of serotonergic drugs." However, many such events do not result in the

serotonin syndrome. Clarification of the predisposing causes and risk groups is necessary.

5. The safety and efficacy of activated charcoal in the prevention or mitigation of SSRI-induced adverse effects should be clarified.

Disclosures

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.

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Appendix 1

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Appendix 2

Grades of Recommendation and Levels of Evidence

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

Appendix 3

Secondary Review Panel Organizations

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Pharmacists Association
American Public Health Association
American Society of Health-System Pharmacists
Association of Maternal and Child Health Programs
Association of Occupational and Environmental Clinics
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centres

Centers for Disease Control and Prevention – National Center for Injury Prevention and Control
Consumer Federation of America
Consumer Product Safety Commission
Department of Transportation
Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of Emergency Medical Technicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

Appendix 4

Triage Algorithm for SSRI Poisoning in Patients of All Ages

Is suicidal, abuse, or malicious intent suspected?	YES → Refer to emergency department.

NO ↓

Is the home situation of concern (e.g., patient lives alone or family/caregiver seems unreliable)?	YES → Refer to emergency department.

NO ↓

Is the patient manifesting more than mild effects (mild effects include vomiting, somnolence [lightly sedated and arousable with speaking voice or light touch], mydriasis, or diaphoresis)?	YES → Refer to emergency department.

NO ↓

Is the patient therapeutically using the SSRI that was unintentionally taken in overdose and, if yes, did they take more than 5 times their usual single therapeutic dose?	YES → Refer to emergency department.

NO ↓

Is the patient therapeutically naïve to the SSRI that was unintentionally taken in overdose and, if yes, did they ingest more than the following amount of an SSRI (five times an adult initial therapeutic dose)?
  Citalopram: 100 mg
  Escitalopram: 50 mg
  Fluoxetine: 100 mg
  Fluvoxamine: 250 mg
  Paroxetine: 100 mg
  Sertraline: 250 mg
	YES → Refer to emergency department.

NO ↓

Is the patient taking other medications likely to interact with the SSRI and cause serotonin syndrome, such as a monoamine oxidase inhibitor?	YES → Refer to emergency department or provide poison center-initiated follow-up every 2 hours for 8 hours.

NO ↓

Observe at home. Instruct caller to call poison center back if symptoms appear. Consider periodic poison center-initiated follow-up during the first 8 hours after ingestion. Refer to an emergency department if more than mild symptoms develop. Check for drug interactions if multiple substances are involved.