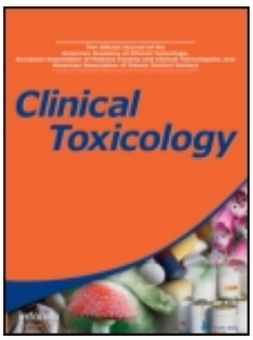

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PRACTICE GUIDELINE

Methylphenidate 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 8,000 ingestions of methylphenidate. 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 out-of-hospital management of patients with suspected ingestions of methylphenidate by 1) describing the process by which a specialist in poison information should evaluate an exposure to methylphenidate, 2) identifying the key decision elements in managing cases of methylphenidate ingestion, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This review focuses on the ingestion of more than a single therapeutic dose of methylphenidate and the effects of an overdose and 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 (Grade D). 2) In patients without evidence of self-harm, abuse, or malicious intent, poison center personnel should elicit additional information including the time of the ingestion, the precise dose ingested, and the presence of co-ingestants (Grade D). 3) Patients who are chronically taking a monoamine oxidase inhibitor and who have ingested any amount of methylphenidate require referral to an emergency department (Grade D). 4) Patients experiencing any changes in behavior other than mild stimulation or agitation should be referred to an emergency department. Examples of moderate to severe symptoms that warrant referral include moderate-to-severe agitation, hallucinations, abnormal muscle movements, headache, chest pain, loss of consciousness, or convulsions (Grade D). 5) For patients referred to an emergency department, transportation via ambulance should be considered based on several factors including the condition of the patient and the length of time it will take for the patient to arrive at the emergency department (Grade D). 6) If the patient has no symptoms, and more than 3 hours have elapsed between the time of ingestion and the call to the poison center, referral to an emergency department is not recommended (Grade D). 7) Patients with acute or acute-on-chronic ingestions of less than a toxic dose (see recommendations 8, 9, and 10) or chronic exposures to methylphenidate with no or mild symptoms can be observed at home with instructions to call the poison center back if symptoms develop or worsen. For acute-on-chronic ingestions, the caller should be instructed not to administer methylphenidate to the patient for the next 24 hours. The poison center should consider making a follow-up call at approximately 3 hours after ingestion (Grade D). 8) Patients who ingest more than 2 mg/kg or 60 mg, whichever is less, of an immediate-release formulation (or the equivalent amount of a modified-release formulation that has been chewed) should be referred to an emergency department (Grade C). 9) If a patch has been swallowed, consider the entire contents of the patch (not just the labeled dose of the patch) to have been ingested. Patients who ingest more than 2 mg/kg or 60 mg, whichever is less should be referred to an emergency department. If it is known that the patch has been chewed only briefly, and the patch remains intact, significant toxicity is unlikely and emergency department referral is not necessary (Grade D). 10) Patients who ingest more than 4 mg/kg or 120 mg, whichever is less, of an

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intact modified-release formulation should be referred to an emergency department (Grade D). 11) For oral exposures, do not induce emesis (Grade D). 12) Pre-hospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present. Do not delay transportation in order to administer activate charcoal (Grade D). 13) Benzodiazepines can be administered by EMS personnel if agitation, dystonia, or convulsions are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (Grade C). 14) Standard advanced cardiac life support (ACLS) measures should be administered by EMS personnel if respiratory arrest, cardiac dysrhythmias, or cardiac arrest are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (Grade C).

Keywords Methylphenidate/poisoning; Poison control centers/standards; Practice guidelines

Introduction

Scope of the problem and importance of the guideline

The majority of children with attention deficit hyperactivity disorder (ADHD) who are treated pharmacologically receive stimulant medication; methylphenidate is the most commonly prescribed stimulant (1). The use of methylphenidate has increased substantially in the US since its approval by the Food and Drug Administration in 1955. Between 1987 and 1996, the proportion of US children up to 18 years of age receiving stimulant medications increased from 0.6 to 2.4% (2). In 2002, 2.9% of children up to 18 years of age, an estimated 2.2 million children, were taking stimulant medications, including 4.8% of those 6–12 years of age (3). In those 19 years of age and older, the use of medications that are prescribed for ADHD rose by 90% between 2002 and 2005 (4).

In 2004, poison centers in the US reported 8,336 human ingestions of methylphenidate to the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers. Of these, 6,035 (72%) were unintentional and 1593 (19%) involved children less than 6 years of age. A total of 940 cases (11%) resulted in moderate toxicity and 73 (0.9%) resulted in major toxicity (5). An analysis of cases reported to TESS between 2000 and 2005 involving children less than 6 years of age found that 460 of 7,833 (5.9%) resulted in moderate effects and 13 (0.2%) resulted in major effects. Between 2000 and 2005, there were only two deaths (17 and 52 years of age), both following abuse of the drug, reported to TESS with methylphenidate as the primary substance.

It is notable that, despite methylphenidate's popularity, only three poison centers reported having methylphenidate guidelines (Table 1). Twelve other centers reported having no guideline for methylphenidate. The other poison centers did not respond to the request for guidelines.

Background on methylphenidate

Methylphenidate is a Schedule II controlled substance approved for the treatment of ADHD and narcolepsy. It also has unlabeled uses in the treatment of depression and to enhance the therapeutic effects of opiates (6).

Table 1. Methylphenidate guidelines used by three US poison centers, 2006

Poison center		
A	If <6 years:	<2 mg/kg rarely causes serious toxicity
	0–5 years:	up to 40 mg well tolerated
	6–12 years:	up to 80 mg well tolerated
B	If <6 years:	refer to emergency department if >2 mg/kg
C	<60 kg:	>1 mg/kg refer to ED
	≥60 kg:	>60 mg refer to ED
	If child's own medication, can observe one extra dose at home	

Pharmacology

It is postulated that methylphenidate's mechanism of action involves increasing dopamine via blockade of dopamine transporters (7). Modulation of norepinephrine may also play a role (8).

Effects following overdose

The manifestations of methylphenidate toxicity are consistent with those of typical sympathomimetic agents. Effects include varying degrees of psychiatric or neurological effects (e.g., headache, CNS excitation or depression, abnormal movements or rigidity, changes in mood or behavior, hallucinations, paranoia), cardiovascular effects (e.g., hypertension, tachycardia, chest pain), and occasionally gastrointestinal effects (e.g., vomiting, abdominal pain) or various laboratory abnormalities (e.g., elevated serum transaminases or creatine kinase, thrombocytopenia). In some cases, hyperthermia, dysrhythmias, and seizures have been reported (9,10).

Adverse reactions

With therapeutic use, suppressed appetite, insomnia, headaches, abdominal pain, nausea, and irritability are common adverse effects (1,9,11). In a study of 47 children aged 5–16 years, Stein et al. (12) found that insomnia and decreased appetite increased in frequency with increasing dose; other adverse effects were not dose related. Additional adverse events unique to chronic therapeutic dosing include weight loss, growth retardation, and perseveration. In addition, methylphenidate can unmask tics in those with Tourette's

syndrome and has been reported to cause hallucinations (9,13). Methylphenidate administration has resulted in an allergic reaction with first-time dosing (14). It is not clear that methylphenidate increases the seizure risk in patients with ADHD who do not have a seizure disorder, and the drug has been used therapeutically in patients with epilepsy without evidence that it lowers the seizure threshold (15,16). New "black-box" warnings address concerns about cardiovascular risk secondary to increases in heart rate and blood pressure documented during chronic use (17). Any further discussion of the risks associated with therapeutic use is beyond the scope of this guideline.

Pharmacokinetics

Formulations for oral methylphenidate include immediate-release (IR), extended-release (ER) and sustained-release (SR), controlled-release osmotic pressure delivery system (OROS), controlled delivery (CD), and LA (extended-release Spheroidal Oral Drug Absorption System). Methylphenidate is also available as a transdermal patch. The patch is designed to be worn 9 hours each day. See Table 2 for a pharmacokinetic comparison of the various products. For the modified-release formulations, crushing or chewing of the tablets destroys the products' modified-release properties. The capsules retain their modified-release properties if opened but not if the beads are crushed.

Methylphenidate demonstrates large pharmacokinetic variability between individuals and in relationships between plasma concentrations and effects (18–21). In one study, the drug displayed nonlinear pharmacokinetics at high doses (20). Metabolism is predominately by de-esterification with 10–20% being metabolized by the hepatic microsomal oxidase system. Its major metabolite, ritalinic acid, is inactive (19,20).

Methylphenidate (d,l-*threo*-methylphenidate) is a racemic mixture of d-methylphenidate and l-methylphenidate. A product approved in November 2001, dexmethylphenidate (Focalin), is the d-*threo* enantiomer of methylphenidate. Dexmethylphenidate and methylphenidate have similar therapeutic properties; dexmethylphenidate is absorbed more completely than methylphenidate (22). Although dexmethylphenidate is described as twice as potent as methylphenidate, the maximum daily dose is not equal to one-half of the maximal daily dose of methylphenidate (20 mg maximum

Table 2. Methylphenidate dosage forms (6,79,80)

Dosage form	Brand name(s)	Strengths available (mg)	Type of modified release	Time to peak plasma concentration	Duration of action
Immediate-release (IR) tablets	Ritalin, Methylin	5, 10, 20	N/A	1–3 hr	1–4 hr
Chewable tablets	Methylin	2.5, 5, 10	N/A	1–2 hr	
Solution	Methylin	5 or 10/5 mL	N/A	1–2 hr	
ER tablets	Metadate ER, Methylin ER	10, 20	wax-matrix extended release	4.7 hr	8 hr
SR tablets	Ritalin-SR	20	wax-matrix resin vehicle sustained release	4.7 hr	8 hr
OROS tablets*	Concerta	27, 36, 54	initial dose (22%) released in 1 hr, remainder released over 5–9 hr	7.7 hr children 6.7 hr adults	12 hr
CD capsules	Metadate CD	10, 20, 30	30% immediate-release beads, remainder extended-release	1st phase 1.5 hr 2nd phase 4.5 hr	8 hr
LA capsules (SODAS†)	Ritalin LA	10, 20, 30, 40	50% immediate release, remainder released 4 hr later	1st phase 2 hr, 2nd phase 6.6 hr children; 5.5 hr adults	8 hr
Patch	Daytrana	10, 15, 20, 30‡	drug in acrylic adhesive dispersed in silicone adhesive patch worn 9 hr each day		

*OROS® = osmotic pressure delivery system, controlled release.
†SODAS® = spheroidal oral drug absorption system.
‡10 mg patch contains 27.5 mg methylphenidate.
15 mg patch contains 41.3 mg methylphenidate.
20 mg patch contains 55 mg methylphenidate.
30 mg patch contains 82.5 mg methylphenidate.

daily dose compared to 60 mg maximum daily dose for methylphenidate). Due to the lack of toxicity information available for this product, it is not discussed further in this guideline.

Drug interactions

Multiple references state that hypertensive crisis might occur if methylphenidate is given with a monoamine oxidase inhibitor (23–25). However, there appears to have been only one published case (in 1964) documenting this reaction (26). In this case, the reaction (described as "hypertensive crisis and hyperventilation syndrome") was stated to occur 15 days after methylphenidate was initiated (7 days after hospital discharge) in a patient receiving tranylcypromine. The recorded blood pressure was 140/90 mmHg. It was not documented that food or other drug interactions were ruled out. Feinberg (27) published a literature review documenting the therapeutic use of methylphenidate and monoamine oxidase inhibitors. This review reported that initial dosages of 5 mg/day of methylphenidate have been utilized in combination with monoamine oxidase inhibitors without adverse effects but suggested that further studies were warranted.

The addition of methylphenidate to the regimens of two children taking valproic acid resulted in dyskinesia and bruxism. The reactions occurred after the second dose (10 mg) in a 4-year-old boy and after the first dose (5 mg) in a 6-year-old girl (28). A pharmacokinetic study in six human volunteers provided evidence that ethanol given with high doses of methylphenidate produces ethylphenidate as a metabolite, which might increase the potential for toxicity (29).

Abuse potential

Published research and case reports have documented the abuse potential of methylphenidate (8,10,30–35). Cases of methylphenidate abuse reported to poison centers in the US increased 7-fold between 1993 and 1999 (10). Routes of abuse include oral administration, nasal insufflation of crushed tablets, and parenteral administration of crushed tablets. Because the pharmacokinetics and subsequent pharmacodynamics of the latter two routes of administration differ markedly from oral ingestion, and because nasal insufflation and parenteral administration carry risks not associated with oral administration (e.g., talc emboli), only cases involving oral administration were considered in formulating this guideline. Problems unique to the abuse of the patch formulation have not yet been described in the literature.

Definition of terms

For the purpose of this guideline, two age groups are defined as either children less than 6 years of age or older children and adults. The older age group is more likely to attempt self-harm and to conceal an exposure. To be consistent with TESS definitions, acute exposures are defined as those occurring over a period of up to 8 hours and chronic exposures are those that occur over a period of more than 8 hours. Acute-on-chronic exposure is an acute exposure in a patient who has already been exposed to methylphenidate for more than 8 hours.

Intended users of this 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 toxicity of methylphenidate is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.

This guideline also provides information for poison center staff members and researchers who wish to further develop the information base available for the development of guidelines for the out-of-hospital management of poisoning.

Objective of this guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial out-of-hospital management of patients with suspected ingestions of methylphenidate by 1) describing the process by which a specialist in poison information should evaluate an exposure to methylphenidate, 2) identifying the key decision elements in managing cases of methylphenidate 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 methylphenidate alone. Ingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances. This review focuses on the ingestion of more than a single therapeutic dose and the effects of an overdose. Although therapeutic use of methylphenidate can sometimes cause adverse effects in adults and children—some idiosyncratic and some dose-dependent—these cases are not considered.

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 (36,37). 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 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.

Search strategy

Literature searches for relevant articles were performed by a single investigator. The National Library of Medicine's PubMed database was searched (through March 2006) using methylphenidate as a MeSH term with the subheadings poisoning (po) or toxicity (to), limited to humans. The PubMed database was further searched using methylphenidate as a textword (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 2006, excluding abstracts of meeting presentations), Science Citation Index (1977–March 2006), Database of Abstracts of Reviews of Effects (accessed March 2006), Cochrane Database of Systematic Reviews (accessed March 2006), and Cochrane Central Register of Controlled Trials (accessed March 2006). Reactions (1980–March 2006), the methylphenidate poisoning management in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, NACCT abstracts published in the Journal of Toxicology Clinical Toxicology (1995–2004) and Clinical Toxicology (2005) were reviewed for original human data.

Five major toxicology textbooks were reviewed for recommendations on the management of methylphenidate poisonings and for citations of additional articles with original human data in the chapter bibliographies. The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from unintentional methylphenidate poisoning. These cases were abstracted for review by panel members. All US poison control centers were surveyed in 2006 to ascertain their out-of-hospital management and triage practices for methylphenidate poisonings.

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, searching specifically for those that dealt with estimations of doses with or without subsequent signs or symptoms of toxicity and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles that did not meet either of the preceding criteria, did not add new data (e.g., reviews, editorials), or that exclusively described inpatient-only procedures (e.g., dialysis) were excluded.

Data extraction process

All articles that were retrieved from the original search were reviewed by a single trained physician abstractor. The complete papers were reviewed for original human data regarding the toxic effects of methylphenidate or original human data directly relevant to the out-of-hospital management of patients with methylphenidate toxicity or overdose. Relevant data (e.g., dose, effects, time of onset of effects, therapeutic interventions or decontamination measures provided, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief description of each article was written. This evidence table is available at http://www.aapcc.org/DiscGuidelines/methylphenidate%20evidence table%202006-7-4.pdf. The table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Efforts were made to locate 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 abstracted articles were made available for reading by the panel members on a secure AAPCC website.

Criteria used to 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 and case series were classified as level 4.

Guideline writing and review

A draft guideline 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, 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 web site or privately through email communication to AAPCC staff. All submitted comments were rendered anonymous, 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 her 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.

Evaluation of evidence

Review of textbooks

A toxic dose for methylphenidate was not found in any of the toxicology textbooks reviewed (38–42).

Poisindex, a computerized toxicology reference used by poison control centers, states that ingestions of less than 1 mg/kg in pediatric patients (age range not defined) have not resulted in toxicity. This statement is not referenced (43).

Review of TESS mortality data

An analysis of the American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database for deaths from ingestion of methylphenidate from 2000 to 2005 found two deaths (17 and 52 years of age). Both involved abuse of the drug, and doses were not reported. In one of the cases, other drugs could not be excluded as contributing to the cause of death.

Review of the literature

Acute ingestions in patients less than 6 years of age

Methylphenidate is not approved for use in patients less than 6 years of age. However, Kratochvil et al. (44) summarized the results of six studies reporting the use of methylphenidate in trials enrolling children with ages ranging from 22 to 71 months (n = 233). The doses ranged from 0.15 to 0.6 mg/kg per dose up to three times daily. Subsequent toxicity was not noted.

There was a level 4 prospective chart review of 49 children less than 6 years of age reported to one poison center over a 3-year period with reported acute ingestions of methylphenidate in which doses of 0.25–10 tablets (0.26–12 mg/kg with a median of 0.9 mg/kg) resulted in what was reported as mild to moderate effects in 24 children. Effects included agitation, irritability, somnolence, vomiting, abdominal pain, and tachycardia. The lowest dose resulting in symptoms in this article was reported to be 0.26 mg/kg with no difference in median dose between those who did and did not develop symptoms. The number of patients who received activated charcoal was not reported. The product was modified-release (type not noted) in nine children and immediate-release in 40; symptom rates were reported as being similar (45). There were also four level 4 or 6 case series and abstracts that included patients less than 6 years of age with reported acute methylphenidate ingestions and from which some dose-toxicity information could be abstracted (46–49). The abstract by Kim et al. (47) was a 2-year retrospective review in which 37 children aged 1–5 years were reported to have ingested methylphenidate. For the 22 cases for which a dose was reported, the mean dose was 1.4 mg/kg (range 0.4–4 mg/kg). Whether the products were immediate-release, extended-release, or sustained-release was not reported. At 1–2 mg/kg, symptoms of hyperactivity and dilated pupils developed in two of 10 children (four received ipecac syrup and three had "gastric decontamination"). The abstract stated that one of two children ingesting 2–4 mg/kg developed symptoms, but the symptoms were not described (both received "gastric decontamination"). The abstract concluded by stating that "serious toxicity" at doses of 2 mg/kg or less in those less than 6 years of age "is uncommon." The meaning of "uncommon" is not known nor is the definition of "serious." White and Yadao (49) published a retrospective review (level 4) of 289 methylphenidate ingestions (patients of all ages) that had been reported to TESS in 1993 and 1994. Only ingestions of immediate-release formulations were included. The doses ingested ranged from 0.06 to 29.3 mg/kg in the 163 cases for which doses were known (mean 1.7 mg/kg). Fourteen of the 126 patients (11%) reported to have ingested up to 2 mg/kg developed moderate effects (defined by TESS). Although the TESS definition of a moderate effect includes isolated seizures, the presence of seizures in any patient in this report was not noted. No major symptoms (defined by TESS) were recorded in this study. Because the definition of a pediatric patient in this study included those up to 18 years of age, it is unknown how many patients were less than 6 years of age. Foley et al. (46) published a case series (level 4) of 113 methylphenidate ingestions (patients of all ages) reported to TESS in 1998; 35 patients were less than 6 years of age. In 24 of the 113 patients, methylphenidate was not the sole substance ingested. The average dose in those less than 6 years of age was 0.94 mg/kg. For the 16% of those less than 6 years who developed symptoms, the mean dose was 0.83 mg/kg. Symptoms reported were drowsiness and hyperactivity. Moderate effects (defined by TESS) were stated to occur in 4% of those in this age group. In the abstract (level 6) by Marquardt et al. (48), 99 of the 329 methylphenidate ingestions reported during 2002 and 2003 occurred in children less than 6 years of age. The presence or absence of symptoms and the mg/kg dose ingested were not delineated by age group. The abstract only notes that, in cases of immediate-release methylphenidate ingestions (all ages), when up to

1 mg/kg was reported to have been ingested, no or minor effects occurred in 50 patients managed with observation only. In cases of intermediate-release methylphenidate ingestion (all ages), when 1–2.2 mg/kg was reported to have been ingested, no or minor effects occurred in 11 patients.

Acute ingestions in patients 6 years of age and older

The therapeutic daily dosage of immediate-release methylphenidate for the treatment of ADHD is 0.3 mg/kg/dose to a maximum of 2 mg/kg/day or 60 mg total, in two divided doses (50). In a study of 37 adults (31.1 ± 6.7 years), doses up to 80 mg/day were safely utilized (up to 90 mg/day was allowed per protocol, but no patient received more than 80 mg) (51). The therapeutic dose of methylphenidate for other indications is the same or lower.

In order to determine if moderate-to-serve toxicity occurred with therapeutic doses, 23 articles (level 1b–2b randomized clinical trials/cohort studies) were reviewed in which multiple doses of methylphenidate were prospectively given to patients at least 6 years of age (12,52–73). There were two randomized trials (level 1b) in which single oral doses of methylphenidate were prospectively given to patients at least 6 years of age that resulted in symptoms not characteristic of expected adverse drug reactions. In the trial by Mulhern et al. (66), three patients developed reactions to the challenge dose of 0.6 mg/kg: a 7-year-old girl became "extremely behaviorally overactive, talkative, and anxious"; a 9-year-old boy developed allergic symptoms requiring treatment with diphenhydramine and a bronchodilator; and an 8-year-old girl developed diplopia, abdominal pain, and leg pain. In the trial by Efron et al. (59), an 11-year-old girl developed "severe headaches" after each dose (0.3 mg/kg) of methylphenidate. A meta-analysis (level 1a) of 62 randomized trials including 2897 patients with ADHD did not report moderate or severe symptoms occurring with therapeutic doses (74).

There were two level 4 case series and one abstract (level 6) that included patients 6 years of age or older with acute methylphenidate ingestions and from which some dose-toxicity information could be abstracted (46,48,49). White and Yadao (49) published a case series of 289 reported ingestions of methylphenidate (patients of all ages) reported to TESS during 1993 and 1994. Ingestions of modified-release methylphenidate formulations were excluded. The doses reportedly ingested ranged from 0.06 to 29.3 mg/kg in the 163 cases for which a dose was known (mean 1.7 mg/kg). Because the pediatric age group was defined in this study up to 18 years of age, it is unknown how many of the patients were 6 years of age or older. Fourteen of the 126 patients (11%) reported to have ingested up to 2 mg/kg developed moderate effects (defined by TESS). Although the TESS definition of a moderate effect includes isolated seizures, the presence of seizures in any patient in this report was not noted. No major symptoms (defined by TESS) were recorded in this study. The most common effects—tachycardia, agitation, and lethargy—were documented in 31% of all cases. No major symptoms were recorded in this study. Foley et al. (42) published a case series of 113 methylphenidate ingestions (patients of all ages) reported to TESS in 1998; 78 patients were 6 years of age or older. In 24 patients, methylphenidate was not the sole substance ingested. The average dose in the 26 patients 6–12 years of age was 0.89 mg/kg while it was 1.7 mg/kg for those 13–19 years old (n = 30). Ranges for these mg/kg doses were not provided. The mean dose was unknown for those more than 19 years of age (n = 22). No major effects were documented. No moderate effects were documented for those 6–12 years of age; moderate effects were reported in 23.3% of those 13–19 years of age (over half of these cases were intentional ingestions) and in 22.7% of those more than 19 years of age (over half of these cases were intentional ingestions). Moderate and major effects were defined by TESS and were not detailed in the article. In the abstract by Marquardt et al. (48), 230 of the 329 methylphenidate ingestions reported during 2002 and 2003 occurred in patients 6 years of age or older. The presence or absence of symptoms and the mg/kg ingested were not delineated by age group. The abstract only notes that in cases of immediate-release methylphenidate ingestions (all ages) when up to 1 mg/kg was ingested, no or minor effects occurred in 50 patients managed with observation only. In cases of intermediate-release methylphenidate ingestions (all ages) when 1–2.2 mg/kg was ingested, no or minor effects occurred in 11 patients, and in cases of long-acting methylphenidate ingestions (all ages) when up to 4 mg/kg was ingested, no or minor effects occurred in 57 patients managed with observation only.

There was one level 4 case report in which a 15-year-old girl in a secure unit was given a methylphenidate 10 mg tablet by another resident. She developed hallucinations followed by respiratory arrest. Upon resuscitation, she had a weak pulse and was hypertensive and hyperthermic. Urine toxicological screening ruled out methylenedioxymethamphetamine and other drugs (75).

Acute-on-chronic ingestions

Acute-on-chronic ingestions in patients less than 6 years of age

White and Yadao (49) reported that six of their patients less than 6 years of age developed symptoms following therapeutic errors; doses were not reported. The most frequently recorded symptoms were lethargy, agitation, headache, and vomiting. Dystonia was seen in one child; two children developed agitation along with tachycardia or hypertension. The abstract (level 6) by Marquardt et al. (48) did not include patient ages in its discussion of 142 acute-on-chronic ingestions. The abstract simply noted that double doses of long-acting methylphenidate formulations up to 4 mg/kg resulted in no or minor effects in 58 patients. It is

unknown how many patients in the abstract (level 6) by Kim et al. (47) had acute-on-chronic ingestions. The case series by Foley et al. (46) did not provide specific outcome information for those with acute-on-chronic exposures. The demographic study (level 4) by Klein-Schwartz (76) stated that 21% of all moderate effects and 30% of all major effects were in children aged 0–12 years ingesting their own medication and that 41% of those with acute-on-chronic ingestions were symptomatic. No information was provided on the acute mg/kg doses or on the specific symptoms that developed.

Acute-on-chronic ingestions in patients 6 years of age and older

White and Yadao (49) reported that for patients 6–11 years of age, 29 (21%) developed symptoms following therapeutic errors (level 4). For those 12–20 years of age, 19 (16%) developed symptoms, and 14 of those more than 20 years old (29%) developed symptoms. Symptoms occurred in 22% (n = 68) of patients with ingestions resulting from therapeutic errors; reported symptoms included agitation (32%), lethargy (17%), vomiting (11%), hypertension (6%), dystonia (6%), tachycardia (6%), and headache (6%). It is unknown whether these percentages represented the proportion of all therapeutic error patients who developed these symptoms or only the proportion of the therapeutic error patients who became symptomatic who developed these symptoms. An mg/kg dose range or mean was not provided for the therapeutic error data. While the authors described reasons for methylphenidate ingestion, the number of therapeutic error patients who developed symptoms and their mg/kg doses were not reported. The abstract (level 6) by Marquardt et al. (48) did not report ages in its discussion of 142 acute-on-chronic ingestions. It noted that double doses of long-acting methylphenidate formulations that totaled 4 mg/kg or less (n = 58) resulted in no or minor effects in 57 patients. The study by Klein-Schwartz and McGrath (10), which looked at all methylphenidate ingestions between 1993 and 1999 in patients up to 18 years of age, stated that 41% of patients (923 of 2,259) with ingestions determined to be acute-on-chronic developed symptoms and that that 21% of all moderate effects and 30% of all major effects were in children up to 12 years of age ingesting their own medication. No information was provided on the acute mg/kg doses or on the specific symptoms that developed.

Onset of effects after acute ingestions

The expert consensus panel members considered the time of onset for toxicity to develop after methylphenidate ingestion to assist decision-making about out-of-hospital management. All articles with toxicity information were searched for estimates of times of onset.

Only three reports provided some data relating to onset of effects. In the case series (level 4) by Bailey et al. (45), all patients were documented as having no symptoms at the time of follow-up. The last follow-up time ranged from 4 to 10 hours after the exposure. In the abstract by Marquardt et al. (48), which evaluated immediate-release (n = 139), intermediate-release (n = 38), and long-acting (n = 152) methylphenidate ingestions, the results section stated that "most cases" had symptom onsets within 6 hours while the conclusion section stated that all symptoms occurred within 6 hours. In two cases in which symptoms occurred when methylphenidate was added to valproic acid therapy, times to symptom onset were 3.75 and 1.5 hours (28).

It should be noted that for the CD, OROS, and LA formulations, between 22 and 50% of the methylphenidate dose is released immediately with the remainder being released over varying periods of time (6). Therefore, while the duration of effect might be dependent on the dosage formulation involved, the time to onset of symptoms might not be affected by the dosage form.

Onset of effects with acute-on-chronic ingestions

In the abstract by Marquardt et al. (48), 142 of the 329 ingestions were classified as acute-on-chronic. For all exposure types (reason for exposure not delineated), the results section stated that "most cases" had symptom onsets of 6 hours while the conclusion section states that all symptoms occurred within 6 hours. As stated above, this time frame most likely reflects follow-up time and is not a reflection of actual time to symptom onset.

Treatment measures

Gastrointestinal decontamination

There were no controlled in vitro or in vivo studies examining the use of ipecac syrup, gastric lavage, or activated charcoal.

Several of the case series reported that gastrointestinal decontamination was performed. The case series (level 4) by Bailey et al. (45) did not report how many patients actually received activated charcoal. Foley et al. (46) noted that 11 patients 19 years of age or younger received activated charcoal (one along with gastric lavage), but the methylphenidate doses ingested by these patients were not reported (level 4). In addition, it is not possible to determine whether patient outcomes were affected. The authors noted that four of the 35 patients less than 6 years of age received activated charcoal and that none of the four developed symptoms. White and Yadao (49) reported that 105 of their 289 patients received gastric decontamination and that outcomes were known for 74 of these patients (level 4). Although the author stated that improved outcomes were not noted, the times from ingestion to gastrointestinal decontamination were not reported nor were the types of decontamination received. The abstract (level 6) by Marquardt et al. (48) noted that 91 patients (28%) received activated charcoal, but it cannot be determined

whether outcomes were changed. In the abstract (level 6) by Kim et al. (47), gastric decontamination was not defined for those treated in healthcare facilities, so it is not known if ipecac syrup, gastric lavage, or activated charcoal was used.

Other therapies

There were no controlled studies examining the use of specific treatments or antidotes for methylphenidate. The use of various treatments, most of them supportive or symptomatic, such as resuscitation, sedation, antipsychotics, or antiepileptics, was reported by several authors describing toxicity following intentional ingestions (level 4), but their efficacy could not be determined from the articles because of insufficient documentation, lack of appropriate controls, difficulties in distinguishing improvement from the natural course of toxicity, and the concurrent use of multiple therapies or therapeutic interventions (30,46,75,77).

Limitations of the literature

A major limitation is the paucity of information. Information available to determine a mg/kg toxic dose of methylphenidate following oral exposures is limited to five chart review studies conducted at poison centers (three published and two in abstract form only) and one case report (45–49,75). With the exception of the prospective case series by Bailey et al. (45), all of the case series were retrospective chart reviews; conclusions could be incorrect due to missing information. The possibility of inaccurate histories provided to poison centers must always be considered. As with the majority of studies reviewing cases of reported toxic ingestions, doses ingested cannot be confirmed. Three of the five case series (46,48,49) included intentional exposures (self-harm and abuse); for these cases, confirming the accuracy of the reported dose ingested is even more problematic. An additional limitation is that the studies, with the exception of the abstract by Marquardt et al. (44), did not separate patients who received gastrointestinal decontamination and, therefore, it is unknown whether decontamination had an effect (45–47,49). None of the three level 4 case series was specifically intended to determine the mg/kg toxic dose of methylphenidate (45,46,49). While mean mg/kg ingested doses were calculated (the case series by Foley et al. [46] and the abstract by Kim et al. [47] did not differentiate between IR, SR, and ER formulations, and the case series by Bailey et al. [45] did not differentiate between IR, SR, ER, OROS, CD, and LA formulations), the primary purpose of these studies was to profile methylphenidate exposure demographics and outcomes. Therefore, symptoms were presented as numbers of patients having symptoms or the percentage of patients having a given symptom. Consequently, determining which specific symptoms were associated with any mg/kg dosage range was not possible. In one of the three case series (49) and one of the two abstracts (48), it was not possible to separate the mg/kg toxic doses between those less than 6 years of age and those 6 years of age and older. This limits the ability to determine if there is a threshold dose at which toxicity is likely to occur. With the exception of a statement in an abstract that hyperactivity and dilated pupils were noted in the two patients who reportedly ingested 1–2 mg/kg (47), none of the published reports provided a description of the adverse effects associate with a given mg/kg dose reported. All that was reported was the total number or the percentage of patients who developed a specific symptom. This is problematic when trying to use the data to make decisions on home management, because one is not able to determine from the data how many children or adults developed symptoms not appropriate for home observation at a given mg/kg ingested dose.

Another limitation of the literature is the lack of toxic dose information for the CD, OROS, and LA formulations of methylphenidate. With the exception of the abstract by Marquardt et al. (48) and the case series by Bailey et al. (45), the studies were conducted during years in which the CD, OROS, and LA formulations were not on the market. In the level 4 report by Bailey et al. (45), the mean mg/kg doses reported did not differentiate between IR, SR, ER, OROS, CD, or LA formulations. This leaves the abstract by Marquardt et al. (48) as the only information available on the toxic dose of modified-release formulations. For the 152 CD, OROS, and LA ingestions described in this abstract, outcomes were only described for 57 cases in which double doses had been taken. Mean doses for all three products (CD, OROS, and LA) were combined into one mean mg/kg dose despite the different release rates of these formulations.

Information on the toxic dose of the SR and ER formulations of methylphenidate are confined to the abstract by Marquardt et al. (48) in which 38 ingestions of SR or ER products were reported; however, only 11 were treated with observation alone. Kim et al. (47) and Foley et al. (46) did not differentiate mean mg/kg toxic doses between the immediate-release formulations and the SR or ER formulations. The report by White and Yadao (49) only included ingestions of immediate-release products.

There are no data on the consequences of methylphenidate patch ingestion. It is unknown how chewing the patch would affect drug delivery.

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 with a known methylphenidate poisoning. These variables include the patient's intent, dose and formulation of the product, the presence of symptoms, and time of ingestion. 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 of methylphenidate, or in whom a malicious intent was suspected (e.g., child abuse or neglect) should be expeditiously transported to an emergency department, regardless of the dose ingested. Patients without these characteristics (e.g., adults with definite unintentional ingestion or children below the age of 6 years in whom abuse is not suspected) are candidates for more selective referral to healthcare facilities.

Dose and formulation

The estimation of dose is based largely on the patient's history and the type of product and its packaging (when available for evaluation). If precise data for the ingestion are unknown or unclear (i.e., package size, unit size, number of units ingested), poison centers often utilize a method in which the maximum potential dose is calculated. For example, if the actual dose ingested cannot be ascertained, the amount of the drug product that is missing from the container is multiplied by the concentration of the formulation.

There is no evidence in the literature that the toxic dose is different depending on the age of the victim; therefore, the panel did not use age to differentiate the toxic dose of methylphenidate.

For asymptomatic patients with acute, unintentional ingestions of immediate-release methylphenidate, the expert consensus panel concluded that home observation is suitable for those ingesting an acute or a single acute-on-chronic dose of up to 2 mg/kg or 60 mg, whichever is less. This is equivalent to the maximum daily dose for methylphenidate that has been documented to be safe and is a dose not associated with moderate or major toxicity in the published abstract by Kim et al. (47). Since some patients might develop dystonias or other non-life-threatening symptoms that would require therapeutic intervention, the caller should be instructed to call back if symptoms develop. It is recommended that the poison center conduct a follow-up call approximately 3 hours after ingestion. For those with acute-on-chronic ingestions, the patient should avoid taking any doses scheduled for the next 24 hours. If a modified-release tablet or the beads from the LA formulation have been chewed, the dose should be calculated as if it was an immediate-release formulation. Since no information is currently available, the panel recommends considering the entire patch contents (not just the labeled dose of the patch; see Table 2) to have been ingested if a patch is swallowed. If it is known that the patch has been chewed only briefly, and the patch remains intact, significant toxicity is unlikely.

For modified-release formulations, the expert consensus panel concluded that home observation might be suitable for those ingesting an acute or a single acute-on-chronic dose of up to 4 mg/kg or 120 mg, whichever is less, as long as the formulation has not been chewed or crushed. Since the most that is promptly released from any of the modified-release formulations is 50% of the dose, doubling the toxic dose set for the immediate-release methylphenidate products seemed prudent and is consistent with the abstract published by Marquardt et al. (48).

The literature does not support a definite drug interaction between methylphenidate and monoamine oxidase inhibitors. However, given the clinical significance of hypertensive crisis, the panel decided that patients who are chronically taking a monoamine oxidase inhibitor (MAOI) and who have ingested any amount of methylphenidate should be referred to an emergency department for evaluation. A minimum observation time cannot be established as the timeframe in which such a reaction would be expected to occur is not known.

Presence of symptoms

For a patient with demonstrated unintentional methylphenidate ingestion, medical evaluation in an emergency department is warranted if the patient has symptoms of moderate to severe toxicity. Examples of moderate to severe symptoms that warrant referral include moderate-to-severe agitation, hallucinations, abnormal muscle movements, loss of consciousness, and convulsions.

Time of onset of toxicity after overdose

Although the abstract of 329 cases by Marquardt et al. (48) noted that symptoms appeared within 6 hours, a more precise time to symptom onset was not provided. The panel concluded that symptoms were most likely to occur within 3 hours of the ingestion. This is based upon the time to peak serum concentrations of methylphenidate (Table 2).

Because the amount of immediate-release drug in the OROS, CD, and LA formulations is 22%, 30%, and 50%, respectively (Table 2), the panel concluded that symptoms were still most likely to occur within 3 hours of the ingestion.

Pregnancy

Methylphenidate is a pregnancy Category C medication. No acute toxicity information in pregnant patients is available nor is any information available on the adverse effect profile of single therapeutic doses in pregnant women.

Potential out-of-hospital management

There is no published evidence from which to make conclusions regarding out-of-hospital managements that might be appropriate in this setting. There is a lack of information to determine whether outcomes are altered after activated charcoal administration. The risk-to-benefit ratio of pre-hospital activated charcoal for gastrointestinal decontamination in methylphenidate poisoning is unknown. Pre-hospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present.

The panel concluded that benzodiazepines can be administered by EMS personnel if agitation, dystonia, or convulsions are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight. The panel also concluded that standard advanced cardiac life support (ACLS) measures should be administered by EMS personnel if respiratory arrest, cardiac dysrhythmias, or cardiac arrest are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (78).

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 (Grade D).
2. In patients without evidence of self-harm, abuse, or malicious intent, poison center personnel should elicit additional information including the time of the ingestion, the precise dose ingested, and the presence of co-ingestants (Grade D).
3. Patients who are chronically taking a monoamine oxidase inhibitor and who have ingested any amount of methylphenidate require referral to an emergency department (Grade D).
4. Patients experiencing any changes in behavior other than mild stimulation or agitation should be referred to an emergency department. Examples of moderate to severe symptoms that warrant referral include moderate-to-severe agitation, hallucinations, abnormal muscle movements, headache, chest pain, loss of consciousness, or convulsions (Grade D).
5. For patients referred to an emergency department, transportation via ambulance should be considered based on several factors including the condition of the patient and the length of time it will take for the patient to arrive at the emergency department (Grade D).
6. If the patient has no symptoms, and more than 3 hours have elapsed between the time of ingestion and the call to the poison center, referral to an emergency department is not recommended (Grade D).
7. Patients with acute or acute-on-chronic ingestions of less than a toxic dose (see recommendations 8, 9, and 10) or chronic exposures to methylphenidate with no or mild symptoms can be observed at home with instructions to call the poison center back if symptoms develop or worsen. For acute-on-chronic ingestions, the caller should be instructed not to administer methylphenidate to the patient for the next 24 hours. The poison center should consider making a follow-up call at approximately 3 hours after ingestion (Grade D).
8. Patients who ingest more than 2 mg/kg or 60 mg, whichever is less, of an immediate-release formulation (or the equivalent amount of a modified-release formulation that has been chewed) should be referred to an emergency department (Grade C).
9. If a patch has been swallowed, consider the entire contents of the patch (not just the labeled dose of the patch) to have been ingested. Patients who ingest more than 2 mg/kg or 60 mg, whichever is less should be referred to an emergency department. If it is known that the patch has been chewed only briefly, and the patch remains intact, significant toxicity is unlikely and emergency department referral is not necessary (Grade D).
10. Patients who ingest more than 4 mg/kg or 120 mg, whichever is less, of an intact modified-release formulation should be referred to an emergency department (Grade D).
11. For oral exposures, do not induce emesis (Grade D).
12. Pre-hospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present. Do not delay transportation in order to administer activate charcoal (Grade D).
13. Benzodiazepines can be administered by EMS personnel if agitation, dystonia, or convulsions are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (Grade C).
14. Standard advanced cardiac life support (ACLS) measures should be administered by EMS personnel if respiratory arrest, cardiac dysrhythmias, or cardiac arrest are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (Grade C).

These recommendations are summarized in Appendix 4.

Implications for research

The panel identified the following topics where additional research is needed or analysis of existing databases might be useful.

1. The toxic dose of immediate-release methylphenidate products in children and adults needs to be verified.
2. The toxic dose of modified-release methylphenidate products in children and adults needs to be verified. This research should differentiate between the SR, ER, OROS, CD, and LA formulations.

3. The toxic dose of transdermal methylphenidate needs to be determined.
4. The toxic dose of ingested methylphenidate patches needs to be determined.
5. The ability of activated charcoal to bind methylphenidate and the extent to which it is adsorbed needs to be verified.
6. The maximum time to onset of symptoms following a toxic ingestion for immediate- and modified-release formulations needs to be verified.
7. The signs and symptoms seen following toxic ingestions of methylphenidate need to be described in case-specific detail.
8. The toxicity profile and toxic dose of methylphenidate in pregnant patients needs to be established.
9. The adverse event profile in patients who therapeutically receive methylphenidate and monoamine oxidase inhibitor combination therapy, or who unintentionally ingest a combination of methylphenidate and a monoamine oxidase inhibitor, needs to be established.
10. The toxic dose of dexmethylphenidate needs to be determined in addition to determining whether its time to onset of effects and signs and symptoms seen following overdose are similar to those of methylphenidate.

Disclosures

Dr. Booze's husband is employed by AstraZeneca. Dr. Erdman was employed by AstraZeneca during his contribution to the development of this guideline. There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

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Appendix 1

Expert consensus panel members

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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 methylphenidate poisoning

Is suicidal intent, self-harm, or malicious administration by another person 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 currently taking a monoamine oxidase inhibitor (MAOI)?	YES → Refer to emergency department.
NO ↓	
Is the patient having moderate to severe symptoms? Examples of moderate to severe symptoms that warrant referral include moderate-to-severe agitation, hallucinations, abnormal muscle movements, headache, chest pain, loss of consciousness, or convulsions.	YES → Refer to emergency department
NO ↓	
Has more than 3 hours passed since the time of ingestion?	YES → No further treatment is necessary. Follow-up with the patient if symptoms are present to make sure they have resolved.
NO ↓	
Did the patient ingest: 1) >2 mg/kg or >60 mg, whichever is less, of an immediate-release formulation, or 2) >2 mg/kg or >60 mg, whichever is less, of a modified-release formulation that has been chewed, or 3) >2 mg/kg or 60 mg, whichever is less, of a patch that has been swallowed (consider the entire contents of the patch, not just the labeled dose of the patch, to have been ingested*)?	YES → Refer to emergency department.

NO ↓

Did the patient ingest >4 mg/kg or >120 mg, whichever is less, of an intact modified-release formulation?

YES → Refer to emergency department.

NO ↓

A follow-up call is recommended at approximately 3 hours after ingestion. Instruct caller to call back prior to the follow-up call if symptoms occur.

For acute-on-chronic ingestions, instruct the caller or patient to avoid taking any further doses of methylphenidate for the next 24 hours.

*If patch has been briefly chewed and is removed from the mouth intact, referral is not necessary.