

Methylphenidate intoxications in children and adults: exposure circumstances and evidence-based dose threshold for pre-hospital triage

Laura Hondebrink, Saskia J. Rietjens, Claudine C. Hunault, Rob R. Pereira, Nuriye Kelleci, Gulhan Yasar, Ariam Ghebreslasie, Cindy Lo-A-Foe, Irma De Vries & Jan Meulenbelt

To cite this article: Laura Hondebrink, Saskia J. Rietjens, Claudine C. Hunault, Rob R. Pereira, Nuriye Kelleci, Gulhan Yasar, Ariam Ghebreslasie, Cindy Lo-A-Foe, Irma De Vries & Jan Meulenbelt (2015) Methylphenidate intoxications in children and adults: exposure circumstances and evidence-based dose threshold for pre-hospital triage, *Clinical Toxicology*, 53:3, 168-177, DOI: [10.3109/15563650.2015.1004579](https://doi.org/10.3109/15563650.2015.1004579)

To link to this article: <http://dx.doi.org/10.3109/15563650.2015.1004579>



View supplementary material [↗](#)



Published online: 04 Feb 2015.



Submit your article to this journal [↗](#)



Article views: 415



View related articles [↗](#)



View Crossmark data [↗](#)

POISON CENTRE

Methylphenidate intoxications in children and adults: exposure circumstances and evidence-based dose threshold for pre-hospital triage

LAURA HONDEBRINK,^{1*} SASKIA J. RIETJENS,^{1*} CLAUDINE C. HUNAUULT,¹ ROB R. PEREIRA,² NURIYE KELLECI,¹ GULHAN YASAR,¹ ARIAM GHEBRESLASIE,¹ CINDY LO-A-FOE,¹ IRMA DE VRIES,¹ and JAN MEULENBELT^{1,3,4}

¹National Poisons Information Center, University Medical Center Utrecht, the Netherlands

²Paediatric Consultancy Hilligersberg, Rotterdam, the Netherlands

³Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

⁴Department of Intensive Care Medicine, University Medical Center Utrecht, the Netherlands

Context. Methylphenidate intoxications mostly have a relatively mild course, although serious complications can occur. **Objective.** We aimed to characterize methylphenidate exposures and reassess our current dose threshold for hospital referral (2 mg/kg). **Methods.** In a prospective follow-up study, we analysed 364 consecutive methylphenidate exposures that were reported to the Dutch Poisons Information Center. Patients and/or physicians were surveyed by telephone using standardized questionnaires. Three physicians independently scored the observed severity of the intoxication of each patient as 'no/mild' (observation at home) or 'moderate/severe' (hospital referral necessary). **Results.** Unintentional exposures (40%) mostly occurred at home involving the patients' own medication or those from a family member. Compared to unintentionally exposed patients, intentionally exposed patients were exposed to relatively high methylphenidate doses (3.1 vs 1.6 mg/kg), more often used immediate release methylphenidate formulations (62 vs 34%) and more frequently had concomitant exposures (71 vs 17%). Severe symptoms like convulsions or coma were reported only in patients with concomitant exposures. Following exposure to methylphenidate only (i.e. no concomitant exposures), the most commonly reported symptoms were dry mucosa, headache, agitation, sleepiness and tachycardia. Our results show that the reported methylphenidate dose is predictive of the observed severity of the intoxication and can therefore aid in pre-hospital triage. **Conclusion.** We increased our current dose threshold for hospital referral from 2 to 3 mg/kg. In addition, we will refer patients at lower doses when clinical symptoms indicate the need for hospital referral. Application of this new dose threshold optimizes triage, thereby reducing unnecessary hospital referral and thus costs, without jeopardising patient safety.

Keywords Abuse; ADHD; Poisoning; Ritalin; Toxicity

Abbreviations ADHD, Attention deficit hyperactivity disorder; DPIC, Dutch Poisons Information Center; NPDS, National Poison Data System; US, United States

Introduction

Attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder which is characterised by the presence of inattention, impulsivity and hyperactivity.¹ Worldwide, the prevalence of ADHD in children is 8–11% and it persists into adulthood in more than 50% of patients.^{2,3} In Europe, the preferred choice of medication for treating ADHD is methylphenidate,² which is available in modified- and

immediate-release formulations with distinct pharmacokinetic profiles.³ Methylphenidate significantly blocks dopamine and norepinephrine transporters in the brain, thereby inhibiting dopamine and norepinephrine recycling, resulting in increased levels of these neurotransmitters.^{4,5}

In the United States (US), the amount of methylphenidate prescriptions to paediatric patients remains constant at a level of approximately 10 million yearly (2002–2010).⁶ In the Netherlands (approximately 17 million inhabitants), an annual increase in methylphenidate prescriptions has been observed over several years and approximately 1 million methylphenidate prescriptions were dispensed in 2012.^{7,8} In addition, the number of annual inquiries regarding a possible methylphenidate intoxication has increased fivefold at the Dutch Poisons Information Center (DPIC) during the last decade. Many patients with a possible methylphenidate intoxication are referred to hospital; in the US, yearly more

Received 5 September 2014; accepted 2 January 2015.

*Both authors contributed equally.

Address correspondence to Saskia Rietjens, PhD, University Medical Center Utrecht, Division of Anaesthesiology, Intensive Care and Emergency Medicine, National Poisons Information Center (NPIC), P.O. box 85500, 3508 GA Utrecht, The Netherlands. Tel: +31-887559542. E-mail: S.Rietjens@umcutrecht.nl

than 30,000 emergency department visits involve exposures to stimulant medications for ADHD. The costs for society are significant; the median US hospital charges per paediatric patient admitted to hospital were estimated at \$6000.⁹ Non-medical use of methylphenidate is also reported, especially amongst students, e.g. to improve academic performance (for review see Bogle and Smith, 2009).¹⁰

Apart from case reports, most data on methylphenidate exposures originate from the National Poison Data System (NPDS), the US poison centres database. Although only half of these cases are followed up,¹¹ studies on methylphenidate exposures using the NPDS have reported on large numbers of exposed patients.^{12–14} Previous studies using the NPDS have reported that a significant number of patients developed symptoms following a non-therapeutic methylphenidate exposure, such as agitation, tachycardia and hypertension, likely induced by increased dopamine and norepinephrine levels (for review see Spiller et al., 2013).¹⁵ However, limited data are available on characteristics of non-therapeutic methylphenidate exposures as well as on the relation between the methylphenidate dose and the observed severity of the intoxication. In 2007, an expert consensus panel developed an evidence-based consensus guideline for out-of-hospital management of patients exposed to methylphenidate. This US guideline recommends hospital referral for all patients with (suspected) intentional exposure, regardless of the reported methylphenidate dose. Patients unintentionally exposed to methylphenidate should be referred to hospital more selectively, mostly based on methylphenidate dose: i.e. doses above 2 mg/kg for immediate-release formulations and above 4 mg/kg for modified-release formulations. This guideline indicated that more research is necessary to establish the relationship between methylphenidate dose and clinical effects.¹⁶

The DPIC's guideline for management of patients exposed to methylphenidate is mostly in line with the US guideline, but no differentiation is made between formulations. The current DPIC's methylphenidate dose threshold for hospital referral was set at 2 mg/kg (irrespective of formulation), based on limited data available in literature regarding the relation between methylphenidate dose and the severity of symptoms. However, the maximum recommended therapeutic methylphenidate dose of 1 mg/kg¹⁷ and the relatively mild symptoms reported to the DPIC following methylphenidate exposures above 2 mg/kg raised the hypothesis that our dose threshold overestimates the risk of methylphenidate exposure.

Although severe symptoms following a non-therapeutic methylphenidate exposure are rare,¹³ hospital referral occurs in approximately 40–75% of exposed patients.^{12,13,18} The aim of our prospective study was twofold: (1) to study methylphenidate exposure circumstances, patient characteristics and clinical effects; (2) to assess whether our current methylphenidate dose threshold (2 mg/kg) for hospital referral is too low, and if so, what would be the optimal dose threshold for hospital referral.

Materials and methods

Inclusion and exclusion criteria

In this prospective follow-up study, all consecutive DPIC cases concerning human methylphenidate exposures were included between 12 August 2012 and 11 August 2013. Patients with a methylphenidate prescription and a therapeutic exposure were excluded. To gather as much information as possible, we aimed to interview both the consulting physician and the exposed patient by telephone, generally within one week following the physician's information request at the DPIC. The parent/caregiver was interviewed when patients < 16 years were involved. Only physicians who physically examined the patient (i.e. were able to evaluate the clinical effects) were asked to participate. Physicians who were only contacted by the patient by telephone regarding the unusual methylphenidate exposure, but did not examine their patient, were excluded from the study. In these specific cases, only the (parent/caregiver of the) patient was asked to participate in our study.

Study procedure

During the physician's information request, the physician was asked to participate in the study. All patients were asked to participate via their treating physician. If agreed, the physician provided us with the patients' contact information. Before the actual interview, informed consent of the (parent/caregiver of the) patient was obtained orally (and recorded) after information was provided on the content, duration and confidentiality of the interview and the anonymous processing of the data. The accredited Medical Research Ethics Committee of University Medical Center Utrecht approved this follow-up study.

Data collection

During the study, health care professionals contacting the DPIC for information about methylphenidate intoxications were informed on possible health effects and treatment according to the standard procedure. Hospital referral was based on the current methylphenidate dose threshold of 2 mg/kg of the DPIC and the presence of symptoms. Below the dose threshold of 2 mg/kg, the DPIC's information specialist estimated the exposure as 'no/mild intoxication', indicating that no symptoms or mild, transient and spontaneously resolving symptoms could be expected. In these cases, it was advised that the patient could be observed at home. Above the dose threshold of 2 mg/kg, the exposure was estimated as a potentially 'moderate/severe intoxication', indicating the possibility of a more pronounced, or prolonged course with severe symptoms. In these cases, hospital referral was advised.

Telephone interviews were conducted using standardised questionnaires tailored to physicians and/or patients, with questions on patient characteristics (age, gender, body weight and methylphenidate user/non user), methylphenidate exposure (self-reported dose, formulation and time of exposure),

exposure circumstances (e.g. route of exposure, (un)intentional exposure), concomitant exposures (e.g. self-reported concurrent use of alcohol, drugs and/or other medicines), clinical course (symptoms and laboratory values) and therapy (e.g. gastrointestinal decontamination measures) (see Annex 1 and 2 in Supplementary data for detailed questionnaires to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1004579>). For patients who used methylphenidate therapeutically, the ratio between the abnormal dose and the normal therapeutic dose was calculated. During the interview, physicians had access to the medical record of the involved patient in most cases. When available, hospital discharge letters (processed anonymously) supplemented this information.

Analyses

Combining physician and patient data

A data set – including cases in which the interview was conducted with only the patient or only the physician, and cases in which interviews were conducted with both the patient and the physician – was constructed. In the latter case, these data were processed complementary. When responses of physician and patient contradicted, the response of the physician was analysed in case of objective data, such as heart rate, body temperature and respiratory rate. In case of subjective data, such as exposure circumstances, the response of the patient was analysed. We defined age-related reference values for heart rate, blood pressure, respiratory rate and body temperature (see Supplementary Table 1 to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1004579>), which were established using several sources.^{19–22}

Dose–response relationship

To investigate the dose–response relationship following methylphenidate exposures, a specific subgroup of patients was selected. For this specific analysis, we excluded patients with specific exposure circumstances that could influence the methylphenidate dose or the severity of symptoms, i.e. patients with multiple methylphenidate exposures (defined as more than 1 h between separate methylphenidate exposures), nasal methylphenidate exposures (‘sniffing’) and patients with relevant concomitant exposures. Relevant concomitant exposures are exposures to any amount of alcohol or drugs of abuse. Also, exposures to therapeutic or supratherapeutic doses of benzodiazepines, opioids, antidepressants, antipsychotics, anticonvulsants or cardiovascular medicines were considered as relevant concomitant exposures. Finally, supratherapeutic exposures to ibuprofen, acetaminophen or naproxen were considered as relevant concomitant exposures. Patients with non-relevant concomitant exposures were included in the dose–response relationship analysis, i.e. low (therapeutic) dosages of acetaminophen (4 patients, dose: 8–26 mg/kg), ibuprofen (1 patient, dose: 13 mg/kg), montelukast/beclomethasone (one 2-year-old patient, montelukast: 0.3 mg/kg orally and beclomethasone: 200 µg via inhalation) and vitamins (1 patient, vitamin C:

1 tablet and multivitamins: 1 tablet). Patients with spontaneous emesis or in whom gastrointestinal decontamination was applied were also not selected for the dose–response relationship analysis, as these procedures will reduce the amount of methylphenidate absorbed, and therefore influence the dose–response relationship.

When the exact amount of ingested tablets was uncertain, but a dose range could be estimated by the physician or (the parent/caregiver of) the patient, the lowest dose was considered. In this way, specific symptoms of the patient are attributed to the lowest possible dose of methylphenidate.

Three experienced clinical toxicologists employed at the DPIC (all MD’s) scored the severity of the intoxication of these patients retrospectively, using follow-up data obtained from the telephone interviews. During scoring, these clinical toxicologists had access to the reported symptoms, laboratory values, age and gender of the patient, but were blinded to the methylphenidate dose. The severity of the intoxication of each patient was scored as ‘no/mild’ or as ‘moderate/severe’. A scoring of ‘moderate/severe’ indicates the need for hospital referral, whereas a scoring of ‘no/mild’ indicates no need for hospital referral. The Delphi method was applied in the process of scoring.²³ Each patient was first scored by each clinical toxicologist independently. Subsequently, patients for whom the clinical toxicologists disagreed regarding the severity of the intoxication were discussed in a meeting in order to reach consensus. Agreement between the three clinical toxicologists was evaluated using Cohen’s kappa and was moderate to substantial with kappa values between two raters of 0.53, 0.59 and 0.68.²⁴

Statistics

Descriptive statistics (percentage, median, interquartile ranges and min/max values) were used to provide an overview of patient characteristics, methylphenidate exposure (dose and formulation), exposure circumstances (e.g. patient’s intent) and symptoms. We used logistic regression models to evaluate the predictive ability of the reported methylphenidate dose (in mg/kg) and the formulation (modified release or immediate release) in order to predict the probability of developing a moderate/severe methylphenidate intoxication. First, univariate logistic regression analyses were performed to test only one explanatory variable, either dose or formulation. Second, a multivariate approach was used in which dose was the variable tested, and formulation and ‘user/non-user’ were included in the model as possible confounders. For a binary outcome such as the presence or absence of a moderate/severe intoxication, and the ability to discriminate between two patients with or without a moderate/severe intoxication, is identical to the area under the receiver operating characteristic (ROC) curve (AUC). Sensitivity and specificity, with 95% confidence intervals (CIs) (using the score method incorporating a continuity correction²⁵), were calculated for different methylphenidate dose thresholds. The scoring of the severity of the intoxication (‘no/mild’ or ‘moderate/severe’) by the three clinical toxicologists was considered as the ‘gold standard’ in

the calculation of sensitivity and specificity. Variables were considered significant when p values were ≤ 0.05 . All statistical analyses were conducted using IBM® SPSS® Statistics 20.0.

Results

Inclusions

We received 496 inquiries regarding human methylphenidate exposures during the one-year study period. In 28 patients, the exposure had not occurred or it was a therapeutic dose, resulting in exclusion. Cases lost to follow-up (104 cases) was due to missing contact data, inability to reach the patient/physician or unwillingness of the patient/physician to participate. A total of 364 cases were followed up (Fig. 1). The median time span between methylphenidate exposure and the conduction of the interview with the patient and/or the physician was 4 and 6 days, respectively.

Characteristics of the study population and exposure circumstances

Median age of the patients who were followed up was 18 (range: 1–74) yrs and median dose was 2.3 (range: 0.1–33.9) mg/kg. Tables 1 and 2 describe the characteristics of the study population (i.e. the patients who were followed up). Half of all inquiries concerned children younger than 18 yrs, whereas 30% of the inquiries concerned children younger than 12 yrs. Exposure was unintentional in 40% of all cases and intentional in 59% of all cases. Most exposures occurred orally (95%), although nasal exposures were reported in a small percentage of patients ($n = 14$, 4%). We received no information requests regarding transdermal methylphenidate patches. In the Netherlands, these patches are not available.

Characteristics of the group of patients who were lost to follow-up were extracted from the DPIC's database, in which several parameters are registered by the DPIC's information specialist at the time of the physician's information request. In 53% of the cases, males were involved (42% female and 5% unknown gender). Median age was 20 (range: 2–56) yrs and median dose was 1.8 (range: 0.6–70) mg/kg. Route of exposure was mostly oral (95%), but occasionally nasal

(1%), a combination of oral and nasal (1%) or unknown (3%). Concomitant exposures were recorded in 34% of the cases.

Unintentional exposures

Most unintentional exposures involved modified-release formulations (66%). In younger patients, exploring behaviour that resulted in ingestion of methylphenidate medication (mostly that of a sibling (63%)) was the most common cause of exposure (92% in 0–4 years old children). An administration error was the most common cause in older unintentionally exposed patients (93% in patients older than 13 yrs). These errors were made by the patient him/herself (48%) as well as by the parent or caregiver (44%) and mostly involved the patients' own medication (93%). The median methylphenidate dose in unintentional exposures was 1.6 (range: 0.1–7.6) mg/kg.

Intentional exposures

Intentional exposures (59%) were mostly observed in adults (76%) who were most often exposed to immediate-release formulations (62%). In the majority of exposures, the patients' own medication (76%) was involved. The patients without a methylphenidate prescription obtained methylphenidate mainly from a family member (33%) or friend (18%).

The primary motive for an intentional methylphenidate exposure was a suicide attempt (44%, see Table 1 for other motives). Females are overrepresented in the motive groups: 'suicide attempt', 'stress reduction' and 'performance improvement'. Remarkably, in children of 13–17 yrs, exposure was frequently intentional (65%), and the reason of exposure was mostly 'suicide attempt'.

In general, relatively high levels of methylphenidate exposures were observed. The median methylphenidate dose in intentional exposures was 3.1 (range: 0.3–33.9) mg/kg. In the groups 'impulsive act' and 'suicide attempt' the median dose was 4.1 and 3.4 mg/kg, respectively. Also, relatively high levels of methylphenidate were sniffed ($n = 14$) (median dose: 2.1 mg/kg). These exposures mostly involved males (86%) with a median age of 28 (min–max: 16–40) yrs who used a high dose of primarily immediate-release formulations, mainly to 'feel good' and for 'fun/kick'.

Concomitant exposures

Concomitant exposures were present in 49% of the methylphenidate exposures and were mostly observed in patients with an intentional methylphenidate exposure (Table 1). Higher methylphenidate doses were observed in patients with a relevant concomitant exposure versus those without (median dose: 2.7 mg/kg vs. 2.1 mg/kg, respectively). Of the patients with a relevant concomitant exposure, primarily only medicines (49%) were involved, followed by only alcohol (15%) or a combination of medicines and alcohol (18%). In patients who concomitantly used other medicines,

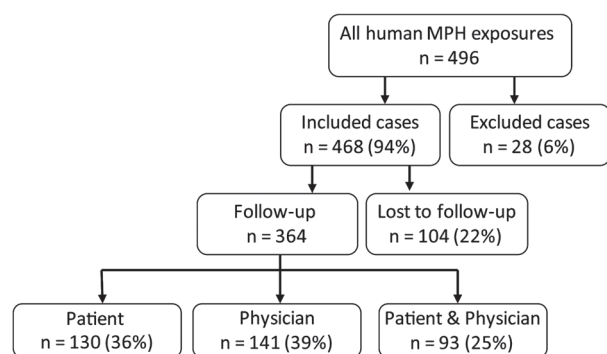


Fig. 1. Number of methylphenidate exposures reported to the DPIC and subsequent follow-up during a one-year study period (2012–2013). MPH: methylphenidate.

Table 1. Patient and exposure characteristics of non-therapeutic methylphenidate exposures reported to the DPIC by reason of exposure.

	All cases ^{a,b} (n = 364)	Unintentional cases ^{a,b} (n = 145)			Intentional cases ^{a,b} (n = 213)					
		Admin. error	Exploring behaviour	Suicide attempt	Feel good	Reduce hyperactivity	Stress reduction	Impulsive act	Performance Improvement	Fun/Kick
Motive	n.r.	95 (66%)	46 (32%)	94 (44%)	20 (9%)	19 (9%)	13 (6%)	13 (6%)	9 (4%)	6 (3%)
Gender ^a										
Male	213 (59%)	76 (80%)	25 (54%)	36 (38%)	14 (70%)	12 (63%)	5 (39%)	7 (54%)	3 (33%)	5 (83%)
Female	151 (41%)	19 (20%)	21 (46%)	58 (62%)	6 (30%)	7 (37%)	8 (62%)	6 (46%)	6 (67%)	1 (17%)
Age (yrs) ^a										
0–4	39 (11%)	2 (2%)	36 (78%)	0	0	0	0	0	0	0
5–12	69 (19%)	55 (58%)	9 (20%)	0	1 (5%)	1 (5%)	0	0	1 (11%)	0
13–17	72 (20%)	22 (23%)	1 (2%)	19 (20%)	2 (10%)	6 (32%)	2 (15%)	5 (39%)	2 (22%)	2 (33%)
18–25	59 (16%)	6 (6%)	0	22 (23%)	9 (45%)	1 (5%)	4 (31%)	2 (15%)	3 (33%)	3 (50%)
26–34	49 (14%)	1 (1%)	0	20 (21%)	4 (20%)	4 (21%)	2 (15%)	3 (23%)	2 (22%)	0
> 35	74 (20%)	9 (10%)	0	31 (33%)	4 (20%)	7 (37%)	5 (39%)	3 (23%)	1 (11%)	1 (17%)
Unknown	2 (1%)	0	0	2 (2%)	0	0	0	0	0	0
Formula ^a										
IR	179 (49%)	19 (20%)	23 (50%)	57 (61%)	15 (75%)	14 (74%)	7 (54%)	9 (69%)	5 (56%)	4 (67%)
MR	145 (40%)	72 (76%)	20 (44%)	24 (26%)	4 (20%)	2 (11%)	4 (31%)	3 (23%)	1 (11%)	1 (17%)
IR & MR	8 (2%)	0	0	3 (3%)	0	1 (5%)	0	0	2 (22%)	0
Unknown	32 (9%)	4 (4%)	3 (7%)	10 (11%)	1 (5%)	2 (11%)	2 (15%)	1 (7%)	1 (11%)	1 (17%)
Source ^a										
Own medicines	264 (73%)	88 (93%)	5 (11%)	72 (77%)	14 (70%)	14 (74%)	9 (69%)	12 (92%)	7 (78%)	4 (67%)
Family	63 (17%)	5 (5%)	37 (80%)	12 (13%)	2 (10%)	2 (11%)	1 (8%)	0	1 (11%)	0
Friend	12 (3%)	0	0	3 (3%)	2 (10%)	1 (5%)	3 (23%)	0	1 (11%)	1 (17%)
Bought	2 (1%)	n.r.	n.r.	0	1 (5%)	1 (5%)	0	0	0	0
Stolen	1 (< 1%)	n.r.	n.r.	1 (1%)	0	0	0	0	0	0
Other	12 (3%)	2 (2%)	4 (9%)	2 (2%)	0	0	0	1 (8%)	0	0
Unknown	10 (3%)	0	0	4 (4%)	1 (5%)	1 (5%)	0	0	0	1 (17%)
Route ^a										
Oral	344 (95%)	95 (100%)	45 (98%)	90 (96%)	14 (70%)	19 (100%)	11 (85%)	13 (100%)	8 (89%)	3 (50%)
Nasal	11 (3%)	0	0	1 (1%)	4 (20%)	0	2 (15%)	0	1 (11%)	1 (17%)
Oral & nasal	3 (1%)	0	0	0	1 (5%)	0	0	0	0	2 (33%)
Unknown	6 (2%)	0	1 (2%)	3 (3%)	1 (5%)	0	0	0	0	0
Location										
At home	287 (79%)	84 (88%)	39 (85%)	67 (71%)	16 (80%)	14 (74%)	10 (77%)	12 (92%)	6 (67%)	3 (50%)
Frequency										
> 1 time	n.r.	n.r.	n.r.	19 (20%)	8 (40%)	7 (37%)	2 (15%)	1 (8%)	3 (33%)	1 (17%)
Conc. exp.										
Present	178 (49%)	19 (20%)	3 (7%)	74 (79%)	14 (70%)	11 (58%)	8 (62%)	6 (46%)	5 (56%)	4 (67%)

Data are presented as n (%).

IR: immediate release; MR: modified release; admin. error: administration error; conc. exp.: concomitant exposure; n.r.: not relevant; n: absolute number of cases. Frequency > 1 time indicates that the patient has intentionally used methylphenidate non-therapeutically more than once.

^aDue to round off, the sum of percentages can be slightly below or above 100%.

^bReason for exposure (unintentional/intentional) was unknown in 2% (n = 6) of the cases. In addition, reason for unintentional exposure and intentional exposure was unknown or did not belong to a listed category in 3% (n = 4) and 18% (n = 39) of the cases, respectively.

antidepressants were most commonly involved (30%), followed by benzodiazepines (27%), analgesics (22%), and antipsychotics (20%).

Symptoms and hospital admission

Severe symptoms like cardiac arrest, cerebral haemorrhage, convulsions or coma were not observed in patients exposed to methylphenidate without concomitant exposures.

To study possible dose–effect relationships, 104 cases of single methylphenidate exposures (29% of the cases with follow-up) were selected for analysis (see Supplementary Table 2 for patients and exposure characteristics to be found at online <http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1004579>). In 62% of these 104 methylphenidate exposures, only the involved patient was interviewed. In 20%

of the cases, only the physician was interviewed and in 18% of the cases, both physician and patient were interviewed. Of these 104 patients, 30 patients were seen at the emergency department and 23 patients were admitted to hospital.

The median reported methylphenidate dose in this group of patients (n = 104) was 1.6 (range: 0.1–16.9) mg/kg and most commonly reported symptoms were agitation (33%), sleepiness (26%), tachycardia (23%), dry mucosa (23%) and headache (20%) (Table 3). Of the patients with agitation, six (18%) also experienced aggression, indicating a higher level of agitation. Table 3 shows the frequencies of symptoms, by dose category (n = 104). Hallucinations, psychosis and arrhythmia were reported only in patients with a reported methylphenidate dose of above 3 mg/kg. The reported symptoms per dose group and formulation are shown in Supplementary Table 3 to be found at online

Table 2. Patient characteristics and exposure circumstances of non-therapeutic methylphenidate exposures reported to the DPIC by age group.

Age group	All ages	0–4 yrs	5–12 yrs	13–17 yrs	18–25 yrs	26–34 yrs	≥ 35 yrs
Patients (n) ^a	364	39	68	72	59	49	74
Gender							
Male	213 (59%)	21 (54%)	57 (84%)	38 (53%)	31 (53%)	24 (49%)	40 (54%)
Female	151 (41%)	18 (46%)	11 (16%)	34 (47%)	28 (47%)	25 (51%)	34 (46%)
Formulation							
IR	179 (49%)	21 (54%)	18 (27%)	24 (33%)	31 (53%)	32 (65%)	51 (69%)
MR	145 (40%)	14 (36%)	47 (69%)	39 (54%)	19 (32%)	8 (16%)	18 (24%)
IR & MR	8 (2%)	0	1 (2%)	2 (3%)	2 (3%)	2 (4%)	1 (1%)
Unknown	32 (9%)	4 (10%)	2 (3%)	7 (10%)	7 (12%)	7 (14%)	4 (5%)
Source							
Own meds	264 (73%)	0	61 (90%)	62 (86%)	47 (80%)	39 (80%)	55 (74%)
Family	63 (17%)	35 (90%)	5 (7%)	4 (6%)	3 (5%)	3 (6%)	12 (16%)
Friend	12 (3%)	0	2 (3%)	3 (4%)	3 (5%)	4 (8%)	0
Bought	2 (< 1%)	0	0	1 (1%)	0	0	1 (1%)
Other	13 (4%)	4 (10%)	0	1 (1%)	2 (3%)	0	5 (7%)
Unknown	10 (3%)	0	0	1 (1%)	4 (7%)	3 (6%)	1 (1%)
Route							
Oral	344 (95%)	38 (97%)	68 (100%)	70 (97%)	54 (92%)	41 (84%)	70 (95%)
Nasal	11 (3%)	0	0	1 (1%)	3 (5%)	5 (10%)	2 (3%)
Oral & nasal	3 (< 1%)	0	0	0	2 (3%)	1 (2%)	0
Unknown	6 (2%)	1 (3%)	0	1 (1%)	0	2 (4%)	2 (3%)
Conc. exposure							
Present	178 (49%)	3 (8%)	9 (13%)	31 (43%)	37 (63%)	36 (74%)	60 (81%)
Origin							
Unintentional	145 (40%)	39 (100%)	64 (94%)	23 (32%)	7 (12%)	2 (4%)	9 (12%)
Intentional	213 (59%)	0	3 (4%)	47 (65%)	52 (88%)	46 (94%)	63 (85%)
Unknown	6 (2%)	0	1 (2%)	2 (3%)	0	1 (2%)	2 (3%)

Data are presented as n (%).

IR: immediate release; MR: modified release; conc. exposure: concomitant exposure; n: absolute number of cases

^aAge was unknown in 0.8% ($n = 3$) of the cases.

<http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1004579>.

Predictive value of the reported methylphenidate dose

The reported methylphenidate dose (mg/kg) was predictive of the observed severity of the intoxication (logistic regression, univariate approach, $\beta = 0.281$, $p = 0.013$, with a discriminative ability (AUC) of 0.70, 95% CI AUC: [0.50, 0.91]). The formulation (modified release or immediate release) was not predictive of the observed severity of the intoxication (logistic regression, univariate approach, $p = 0.45$). When using a multivariate approach, the reported dose (in mg/kg) remains predictive of the severity of the intoxication ($\beta = 0.301$, $p = 0.009$).

To determine the best dose threshold for hospital referral, we determined the sensitivity and specificity, as it is commonly done to determine the predictive value of laboratory tests for a specific outcome or disease. In our data, a methylphenidate dose above or below the dose threshold is the test for the outcome of a 'moderate/severe' intoxication (hospital referral is necessary). This outcome was determined retrospectively by three clinical toxicologists who scored the observed severity by assessing all reported symptoms of each patient using the follow-up data. We then investigated the effect on sensitivity and specificity of different tests, i.e. by applying different dose thresholds for hospital referral

(2, 3, 4 or 5 mg/kg, Table 4). Application of our current dose threshold (2 mg/kg) results in a sensitivity and specificity of 0.60 and 0.61, respectively. Increasing the dose threshold to 3 mg/kg does not alter sensitivity, but increases specificity to 0.85. In addition, increasing the dose threshold from 2 to 3 mg/kg would prevent unnecessary hospital referral. The number of patients with a methylphenidate exposure above the dose threshold for hospital referral but with a mild clinical course ('no/mild intoxication') decreases from 37 to 14 patients (Table 4). Unnecessary hospital referral decreases from 86% (37 out of 43 patients) to 70% (14 out of 20 patients) using a methylphenidate dose threshold of 3 mg/kg instead of 2 mg/kg. Sensitivity and specificity values corresponding to a dose threshold of 4 and 5 mg/kg are also presented in Table 4.

Discussion

In this prospective study we have related the occurrence of symptoms following non-therapeutic methylphenidate exposures to the dose in a large group of patients. The major finding is that, even though the reported methylphenidate dose was usually above therapeutic dose levels, none of the patients exposed only to methylphenidate developed serious symptoms such as rhabdomyolysis, convulsions, cardiac arrest, cerebral haemorrhage or coma. Most frequently reported symptoms were agitation, sleepiness and tachycardia,

Table 3. Reported symptoms and characteristics of patients with non-therapeutic oral methylphenidate exposures, without relevant concomitant exposures, reported to the DPIC by dose group.

Dose	All doses	< 1 mg/kg	1–2 mg/kg	2–3 mg/kg	> 3 mg/kg
Patients (n)	104	25	36	23	20
Median age (yrs)	11	6	10	10	19
Median dose (mg/kg)	1.6	0.6	1.5	2.3	4.9
MR	48 (46%)	4 (16%)	16 (44%)	18 (78%)	10 (50%)
User (patient with methylphenidate prescription)	72 (69%)	10 (40%)	27 (75%)	20 (87%)	15 (75%)
Cardiopulmonary					
Chest pain	1 (1%)	0	0	0	1 (5%)
Tachycardia	23 (22%)	7 (28%)	5 (14%)	5 (22%)	6 (30%)
Arrhythmia	1 (1%)	0	0 (0%)	0	1 (5%)
Hypertension	12 (12%)	2 (8%)	1 (3%)	3 (13%)	6 (30%)
Tachypnoea	6 (6%)	1 (4%)	1 (3%)	0	4 (20%)
Neurological/psychiatric					
Agitation	34 (33%)	13 (52%)	11 (31%)	3 (13%)	7 (35%)
Aggression	6 (6%)	1 (4%)	3 (8%)	1 (4%)	1 (5%)
Confusion	11 (11%)	4 (16%)	2 (6%)	2 (9%)	3 (15%)
Hallucinations	3 (3%)	0	0	0	3 (15%)
Psychosis	2 (2%)	0	0	0	2 (10%)
Hyperreflexia	2 (2%)	0	0	0	2 (10%)
Mydriasis	13 (13%)	1 (4%)	4 (11%)	3 (13%)	5 (25%)
Tremor	12 (12%)	1 (4%)	3 (8%)	3 (13%)	5 (25%)
Other symptoms					
Increased temperature	9 (9%)	1 (4%)	4 (11%)	1 (4%)	3 (15%)
Nausea	13 (13%)	3 (12%)	4 (11%)	3 (13%)	3 (15%)
Headache	21 (20%)	6 (24%)	7 (19%)	5 (22%)	3 (15%)
Sleepiness	27 (26%)	5 (20%)	12 (33%)	7 (30%)	3 (15%)
Dry mucosa	24 (23%)	5 (20%)	7 (19%)	5 (22%)	7 (35%)
Observed severity of intoxication					
None/mild	94 (90%)	24 (96%)	33 (92%)	23 (100%)	14 (70%)
Moderate/severe	10 (10%)	1 (4%)	3 (8%)	0	6 (30%)

Data are presented as n (%).

MR: modified-release formulation; n: absolute number of patients

For this analysis the following patients were excluded: patients with multiple or nasal methylphenidate exposures, patients with spontaneous emesis or in whom gastrointestinal decontamination was applied and patients with relevant co-exposures (see also 'Materials and methods').

in accordance with other methylphenidate overdose case series.^{13,14,26–29}

We showed that the reported methylphenidate dose is predictive of the observed severity of the intoxication ('no/mild' or 'moderate/severe') and can therefore aid in pre-hospital triage. A threshold of 3 mg/kg differentiates patients needing hospital referral from those who do not, better than our current 2 mg/kg threshold.

We observed slightly more intentional than unintentional exposures in the total study population, but in children

(12 yrs and younger) the majority of exposures (96%) were unintentional (Table 2). Previous studies investigating a similar population have shown a lower number of intentional exposures of 25–35%.^{13,14} Most likely, this difference is due to a difference in age distribution between the study populations and the higher occurrence of intentional exposures with an increasing age.

Males were overrepresented in unintentional methylphenidate exposures due to administration errors (80%, Table 1), possibly due to the ratio boy/girl of 3.8 in the use of

Table 4. Sensitivity and specificity corresponding to the use of different methylphenidate dose thresholds to predict the severity of the intoxication.

	Threshold 2 mg/kg		Threshold 3 mg/kg		Threshold 4 mg/kg		Threshold 5 mg/kg	
	≥ 2 mg/kg	< 2 mg/kg	≥ 3 mg/kg	< 3 mg/kg	≥ 4 mg/kg	< 4 mg/kg	≥ 5 mg/kg	< 5 mg/kg
Moderate/severe intoxication ('disease' present)	6	4	6	4	5	5	4	6
No/mild intoxication ('disease' not present)	37	57	14	80	10	84	6	88
Sensitivity [95% CI]	0.60 [0.27;0.86]		0.60 [0.27;0.86]		0.50 [0.20;0.80]		0.40 [0.14;0.73]	
Specificity [95% CI]	0.61 [0.50;0.70]		0.85 [0.76;0.91]		0.89 [0.81;0.95]		0.94 [0.86;0.97]	

The severity of the intoxication was scored for a subset of 104 patients by three physicians based on reported symptoms during follow-up. 95% CIs are indicated between brackets. A scoring of moderate/severe intoxication indicates the need for hospital referral, whereas a scoring of no/mild intoxication indicates no need for hospital referral. Patients with multiple or nasal methylphenidate exposures, patients with spontaneous emesis or in whom gastrointestinal decontamination was applied and patients with relevant co-exposures were excluded for this analysis (see also 'Materials and methods').

psychostimulants in the Netherlands.³⁰ Also, exposure to modified-release formulations was overrepresented in this group amounting up to 76%, a percentage far above the market share of modified-release formulation prescriptions in the Netherlands (47%).³¹ In contrast, lower frequencies of modified-release formulations were observed in intentional exposures. These differences could be due to differences in age distribution between unintentional and intentional exposures combined with the apparent age-dependent exposure to modified-release formulations (Table 2). In addition, modified-release formulations could be prescribed more often to younger, newly ADHD-diagnosed patients since this type of formulations were introduced in the Netherlands in 2003,³⁰ whereas older patients already used an immediate-release formulation.

Most unintentional exposures occurred at home (85%) and the majority of the unintentional exposures were due to administration errors (66%) that involved the patient's own medication (93%, Table 1). For example, in several cases both the father and mother administered methylphenidate to their child. In addition, the tablet belonged to a family member in 80% of unintentional exposures due to exploring behaviour of children (32% of unintentional exposures). Therefore, the use of child-proof organiser boxes could aid in preventing unintentional exposures, since these make it evident whether a dose is already given.

Like others,^{12–14} we observed that most intentional methylphenidate exposures involved a suicide attempt (44%, Table 1). Possibly, some intentional exposures are due to patients using an inadequate methylphenidate dose to control ADHD symptoms. For patients who therapeutically used methylphenidate, the ratio between the abnormal dose and the normal therapeutic dose showed that relatively high amounts of methylphenidate were used. For example, patients used approximately 9 times their therapeutic dose to reduce hyperactivity. Therefore, physicians prescribing methylphenidate should monitor their patients closely for adequate dosing. Notably, motives related to recreational drug use were hardly reported in our study; e.g. the motive 'for fun/kick' was only mentioned in 3% of intentional exposures. Although comparison to other studies is difficult, since terms like 'abuse' and 'misuse' are often not well defined and sometimes also include suicide attempts, others observed a higher amount of abuse, varying from 20 to 40%.^{12,13}

The guideline developed by Scharman et al. for out-of-hospital management of patients exposed to methylphenidate recommends that patients should be referred to hospital at doses above 2 mg/kg for immediate-release formulations and doses above 4 mg/kg for modified-release formulations. Several other criteria were included in this guideline: the patient's intent, the presence of symptoms, methylphenidate formulation, time of ingestion and specific concomitant exposures. For example, all patients with a (suspected) intentional exposure should be referred to an emergency department, regardless of the methylphenidate dose ingested.¹⁶

In the Netherlands, the poisons information centre informs physicians only on the expected severity of the intoxication and the possible somatic treatment. The necessary

psychiatric treatment following intentional exposures is assessed by the treating physician. Therefore, our prospective study was focussed on determining a methylphenidate dose threshold that predicts the severity of the intoxication and can be applied for hospital referral. We showed that the reported methylphenidate dose (mg/kg) is predictive of the observed severity of the intoxication. 'Predictive' means that the probability of a patient having moderate/severe methylphenidate intoxication (the outcome) rises with increasing reported methylphenidate dose. The discriminative ability (AUC) equalled 0.70. An AUC varies between 0.5 (a useless model) and 1.0 (a perfect model). The AUC indicates the probability that, for a randomly chosen pair of patients, one with the outcome and one without, the patient with the highest predicted probability (based on the reported methylphenidate dose) is the one with the outcome. Increasing the dose threshold from 2 to 3 mg/kg does not affect the sensitivity but improves the specificity and thus decreases unnecessary hospital referral (Table 4). Further increasing the dose threshold from 3 to 4 mg/kg would further improve the specificity, but would reduce the sensitivity. Although a sensitivity of approximately 0.6 (using a dose threshold of 2 or 3 mg/kg) appears relatively low, in practice, triage of patients by the DPIC is not just based on the reported dose. Of course, other factors such as the occurrence of severe symptoms and relevant concomitant exposures are also considered by the DPIC during decision making in triage of patients when deciding whether the patient should be sent to hospital. We did not discriminate between different formulations of methylphenidate (modified release and immediate release) in establishing new dose thresholds for hospital referral, as this parameter was not predictive of the severity of the intoxication in the current group of patients in our study.

Our study has some limitations. Twenty-two percent of patients were lost to follow-up. Nevertheless, characteristics of these patients (e.g. dose) were collected at the time of the physician's inquiry and have been reported (see '*Characteristics of the study population and exposure circumstances*'). Although mortality due to methylphenidate overdose in this group of patients cannot be verified, no fatalities linked to methylphenidate overdose were reported at the time of the physician's information request to the DPIC. Also, in general, fatalities associated with methylphenidate overdose are rarely reported and are mostly linked to intravenous or intranasal abuse of methylphenidate.^{32,33} Recently, the first isolated methylphenidate ingestion associated with a fatality has been reported in a 62-year-old woman (57 kg). Although the precise dose ingested was not clear, more than 3 g of methylphenidate medication was missing.³⁴ This is well above the highest dose in our study population (33.9 mg/kg).

Another limitation of our study is that reported symptoms are dependent on the interviewee (patient/physician) which could influence determination of the dose threshold, since not all follow-ups included a survey with both the physician and patient. The symptoms of hospitalised patients were medically confirmed, whereas in the group of patients that were observed at home (the less severe cases) all information was retrieved from the patients themselves, exclusively.

Furthermore, inclusion bias could have occurred, since physicians mainly contact us on uncertainties about possible symptoms and/or treatment. Therefore, severe methylphenidate exposures could be overrepresented in our patient population, although this would not affect the dose–effect relationship and is thus unlikely to affect the determination of a dose threshold. The degree of recall bias is expected to be low, since most patients and physicians were contacted within approximately 1 week after exposure. Furthermore, self-reported dose was used to determine methylphenidate exposure, since blood levels were available in only three patients. Information on concomitant exposures was also based on self-reported data and was not confirmed by drug screening. In the subgroup of 104 patients who were included in determining the dose–response relationship (i.e. those patients orally exposed to methylphenidate, without relevant concomitant exposures and in whom no gastrointestinal decontamination was applied) only 10 patients developed a ‘moderate/severe’ intoxication. A larger sample size would increase the reliability of our results, e.g. rare symptoms like seizures or coma (previously reported prevalence of 0.05–0.08% in methylphenidate exposures)¹³ are likely to remain undetected in our study. Therefore, the need for hospital referral should be based on a threshold dose combined with the observed clinical course. In a future study, we will continue to follow up all methylphenidate exposures above 3 mg/kg (without concomitant exposures), in order to decide whether the threshold of 3 mg/kg for hospital referral can be further increased. Moreover, we aim to gain more insight in differences in dose–response relationships between immediate- and modified-release methylphenidate formulations.

Conclusions

The reported methylphenidate dose is predictive for the severity of the intoxication. Application of a dose threshold can thus aid in decision making for hospital referral of patients exposed to methylphenidate. Of course, the observed clinical course is always of the highest significance in pre-hospital triage and if symptoms are present that indicate the need for hospital referral, these should prevail the methylphenidate threshold dose. Based on our results, we increased our current dose threshold for hospital referral from 2 to 3 mg/kg. Application of this new dose threshold will reduce unnecessary hospital referral and thus costs, without jeopardising patient safety.

Acknowledgements

We gratefully acknowledge M. Leenders (MD) and D. de Lange (MD, PhD) for their effort in rating the severity of the intoxications.

Declaration of interest

Apart from Dr. Pereira, none of the authors have a potential conflict of interest. Those from Dr. Pereira are as follows: chairman of the Dutch ADHD network, payment for

educational presentations (for psychologists at Cure and Care (Arnhem, the Netherlands), up to 2011 also for pharmaceutical companies like Lilly, Janssen, Eurocept and Shire) and royalties of his book ‘ADHD, en nu?’ (ADHD, what now?, ISBN 9021550407).

Congress presentations

Parts of this study have been presented at the annual congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT XXXIII 2013 Copenhagen, and XXXIV 2014 Brussels).

Hondebrink L, Rietjens SJ, Kelleci N, Yasar G, de Vries I, Meulenbelt J. Prospective follow-up study on potential toxic methylphenidate exposures (Abstract EAPCCT XXXIII International Congress). *Clin Toxicol (Phila)* 2013;51(4):298.

Rietjens SJ, Hondebrink L, Hunault CC, Pereira R, Kelleci N, Yasar G, Ghebreslasie A, Lo-A-Foe C, de Vries I, Meulenbelt J. Clinical outcomes of methylphenidate intoxications in children and adults: A prospective follow-up study (Abstract EAPCCT XXXIV International Congress). *Clin Toxicol (Phila)* 2014;52(4):328.

References

1. DSM-V. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, fifth edition, 2013.
2. Hodgkins P, Shaw M, Coghill D, Hechtman L. Amphetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. *Eur Child Adolesc Psychiatry* 2012; 21:477–492.
3. McDonagh MS, Peterson K, Thakurta S, Low A. Drug class review: pharmacologic treatments for attention deficit hyperactivity disorder: final update 4 report [Internet]. Drug Class Reviews 2011.
4. Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. *Biol Psychiatry* 2010; 68:854–860.
5. Volkow ND, Fowler JS, Wang GJ, Ding YS, Gatley SJ. Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: results from imaging studies. *Eur Neuropsychopharmacol* 2002; 12:557–566.
6. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002–2010. *Pediatrics* 2012; 130:23–31.
7. SFK. Stichting Farmaceutische Kengetallen. Explosieve groei ADHD-middelen zet door. *Pharmaceutisch Weekblad* 2008; 143:29–30.
8. SFK. Stichting Farmaceutische Kengetallen. Gebruik ADHD-middelen niet in te tomen. *Pharmaceutisch Weekblad* 2012; 147:30–31.
9. Levine M, Froberg B, Ruha AM, Burns-Ewald M, Yen M, Claudius IA, et al. Assessing the toxicity and associated costs among pediatric patients admitted with unintentional poisonings of attention-deficit/hyperactivity disorder drugs in the United States. *Clin Toxicol (Phila)* 2013; 51:147–150.
10. Bogle KE, Smith BH. Illicit methylphenidate use: a review of prevalence, availability, pharmacology, and consequences. *Curr Drug Abuse Rev* 2009; 2:157–176.
11. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Dart RC. 2010 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol (Phila)* 2011; 49:910–941.
12. Foley R, Mrvos R, Krenzelok EP. A profile of methylphenidate exposures. *J Toxicol Clin Toxicol* 2000; 38:625–630.

13. Klein-Schwartz W. Pediatric methylphenidate exposures: 7-year experience of poison centers in the United States. *Clin Pediatr (Phila)* 2003; 42:159–164.
14. White SR, Yadao CM. Characterization of methylphenidate exposures reported to a regional poison control center. *Arch Pediatr Adolesc Med* 2000; 154:1199–1203.
15. Spiller HA, Hays HL, Aleguas A Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. *CNS Drugs* 2013; 27:531–543.
16. Scharman EJ, Erdman AR, Cobaugh DJ, Olson KR, Woolf AD, Caravati EM, et al. Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2007; 45:737–752.
17. US Food and Drug administration (FDA). Maximum Recommended Therapeutic Dose (MRTD) Database, 2013.
18. Klein-Schwartz W, McGrath J. Poison centers' experience with methylphenidate abuse in pre-teens and adolescents. *J Am Acad Child Adolesc Psychiatry* 2003; 42:288–294.
19. American Heart Association. 2013. http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/About-High-Blood-Pressure_UCM_002050_Article.jsp, consulted January 2013.
20. Derksen-Lubsen G. Compendium Kindergeneeskunde - Diagnostiek en Behandeling. 2011, 4th ed. Houten: Bohn Stafleu van Loghum.
21. El-Radhi AS, Barry W. Thermometry in paediatric practice. *Arch Dis Child* 2006; 91:351–356.
22. Hunter J, Rawlings-Anderson K. Respiratory assessment. *Nurs Stand* 2008; 22:41–43.
23. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; 311:376–380.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33:159–174.
25. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998; 17: 857–872.
26. Backman E, Sjoberg G. Methylphenidate overdose in adolescents and adults - experience in Sweden (Abstract EAPCCT XXVII International Congress). *Clin Toxicol (Phila)* 2007; 45:366.
27. Bailey B, Letarte A, Abran MC. Methylphenidate unintentional ingestion in preschool children. *Ther Drug Monit* 2005; 27:284–286.
28. Koller M, Schnorf-Huber S, Kupferschmidt H, Meier-Abt P. Acute toxicity of oral methylphenidate (MP) overdose in Switzerland (Abstract EAPCCT XXII International Congress). *Clin Toxicol (Phila)* 2002; 40:276.
29. Marquadt K, Alsop J, Lamb JP, Lai C, Walsh M, Albertson TE. Methylphenidate ingestions: comparison of drug formulations (Abstract NACCT Annual Meeting). *Clin Toxicol (Phila)* 2004; 42:728.
30. Trip AM, Visser ST, Kalverdijk LJ, de Jong-van den Berg LT. Large increase of the use of psycho-stimulants among youth in the Netherlands between 1996 and 2006. *Br J Clin Pharmacol* 2009; 67:466–468.
31. SFK. Data obtained from a 2013 data request to SFK. Stichting Farmaceutische Kengetallen 2013.
32. Levine B, Caplan YH, Kauffman G. Fatality resulting from methylphenidate overdose. *J Anal Toxicol* 1986; 10:209–210.
33. Massello W III, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). *J Forensic Sci* 1999; 44:220–221.
34. Cantrell FL, Ogera P, Mallett P, McIntyre IM. Fatal oral methylphenidate intoxication with postmortem concentrations. *J Forensic Sci* 2014; 59:847–849.

Supplementary material available online

Supplementary data for detailed questionnaires and Supplementary Tables 1–3.