

# Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: A first evaluation\*

Erwin Ista, RN, PhD; Monique van Dijk, PhD; Claudia Gamel, RN, PhD; Dick Tibboel, MD, PhD; Matthijs de Hoog, MD, PhD

**Objective:** To establish frequencies of benzodiazepine and opioid withdrawal symptoms, and correlations with total doses and duration of administration.

**Design:** A prospective, repeated-measures design.

**Setting:** Two pediatric intensive care units in a university children's hospital.

**Patients:** Seventy-nine children, aged 0 days to 16 yrs, who received intravenous midazolam and/or opioids for >5 days.

**Interventions:** None.

**Measurements and Main Results:** Pediatric intensive care unit nurses assessed withdrawal symptoms using the Sophia Benzodiazepine and Opioid Withdrawal Checklist, which includes all withdrawal symptoms ( $n = 24$ ) described in the pediatric literature. Over 6 months, 2188 observations in 79 children were recorded. Forty-two percent of observations were performed within 24 hrs after tapering off or discontinuation of medication. Symptoms representing overstimulation of the central nervous system, such as anxiety, agitation, grimacing, sleep disturbance, increased muscle tension, and movement disorder, were observed in >10% of observations. Of symptoms reflecting gastro-

intestinal dysfunction, diarrhea and gastric retention were most frequently observed. Tachypnea, fever, sweating, and hypertension as manifestations of autonomic dysfunction were observed in >13% of observations. The Spearman's rank-correlation coefficient between total doses of midazolam and maximum sum score (of the Sophia Benzodiazepine and Opioid Withdrawal Checklist) was .51 ( $p < 0.001$ ). The correlation between total doses of opioids and the maximum sum score was .39 ( $p < 0.01$ ). A significant correlation (.52;  $p < 0.001$ ) was also found between duration of use and maximum sum score.

**Conclusions:** This is the first study to report frequencies of all 24 withdrawal symptoms observed in children after decrease or discontinuation of benzodiazepines and/or opioids. Agitation, anxiety, muscle tension, sleeping <1 hr, diarrhea, fever, sweating, and tachypnea were observed most frequently. Longer duration of use and high dosing are risk factors for development of withdrawal symptoms in children. (*Crit Care Med* 2008; 36:2427-2432)

**KEY WORDS:** withdrawal symptoms; children; sedation; benzodiazepines; opioids; morphine; pediatric intensive care unit; critical care

Ventilated, critically ill children commonly receive sedatives and analgesic drugs to ease their anxiety, pain, and mental burden induced by the pediatric intensive care unit (PICU) setting. Usually these medications are intravenous opioids and benzodiazepines (1, 2). Long-term exposure to these drugs, however, carries the risk of physical dependence. Abrupt discontinuation or too rapid tapering down of sedatives and analgesics in physically dependent children may result in with-

drawal syndrome (3). High total cumulative doses, long-term infusion (>5-7 days) and too rapid tapering off or abrupt discontinuation of sedatives and/or analgesics have been found to increase the risk of withdrawal syndrome in children in a PICU (4-7).

Symptoms observed in withdrawal syndrome in children include (1): central nervous system irritability (e.g., agitation, anxiety, tremors, increased muscle tension, sleep disturbance, and abnormal movements) (2), gastrointestinal dysfunction (vomiting, diarrhea, and poor feeding) (3), and autonomic dysfunction (e.g., sweating, fever, tachycardia, hypertension, and tachypnea) (4-18).

The reported incidences of benzodiazepine withdrawal syndrome in critically ill children range from 17% to 35% (5, 6). So far, only Katz et al. (7) have documented opioid withdrawal in critically ill children; it was found in 13 of 23 PICU patients (57%) receiving fentanyl.

Diagnosing withdrawal syndrome in PICU patients is a complex matter, be-

cause some symptoms may strongly overlap with clinical signs of inadequate pain or sedation management, ventilator distress, delirium, and stress induced by the noisy environment (19-23). Furthermore, symptoms of benzodiazepine withdrawal largely overlap with those of opioid withdrawal. Yet, we should be able to distinguish between opioid and benzodiazepine related withdrawal, and confounders, as each requires a different treatment approach. Therefore, a clinically validated and sensitive assessment tool is needed to determine the presence and nature of different withdrawal symptoms and their relative frequencies. Such a tool is still lacking (24, 25), leaving aside the Neonatal Abstinence Score developed for infants of drug-dependent mothers (26) which has been used in several studies in critically ill children (7, 11, 13, 27, 28).

Documenting the prevalence of relevant withdrawal symptoms is an essential first step in the development of an assessment tool. To our knowledge, prevalence

**\*See also p. 2479.**

From the Department of Intensive Care Unit (El, Mvd, DT, MdH), Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands; Department of Nursing Science (CG), Utrecht University, Utrecht, The Netherlands.

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For information regarding this article, E-mail: w.ista@erasmusmc.nl

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of the whole spectrum of withdrawal symptoms have not yet been prospectively studied in PICU patients. We therefore conducted a study evaluating all withdrawal symptoms in critically ill children described in the literature and recently reviewed by us (24). A second aim was to establish possible correlations between withdrawal symptoms and total doses of benzodiazepines or opioids and duration of use.

## MATERIALS AND METHODS

**Design.** A prospective, repeated-measures design was used to estimate occurrences of withdrawal symptoms using a self-designed observation form that included withdrawal symptoms described in the literature.

**Patients.** Children aged  $\leq 16$  yrs admitted to the pediatric and pediatric surgical intensive care units of our level III children's hospital between September 2005 and February 2006 were eligible for this study if they received midazolam (a benzodiazepine), morphine, or fentanyl (opioids) by continuous infusion for at least 5 days. These units serve as a referral center for all critical care patients (medical and surgical, 0–16 yrs) except post-operative open heart surgery. Exclusion criteria were: status epilepticus treated with midazolam, use of neuromuscular blocking agents, and severely disturbed behavior pattern on account of underlying neurologic disease.

The Erasmus Medical Center institutional review board reviewed and approved this study. Because of the strictly observational and noninvasive nature of this study, the need for informed consent was waived. The parents of enrolled subjects received an information sheet explaining the study.

Severity of illness was scored using the Pediatric Index of Mortality and the Pediatric Risk of Mortality II (29, 30).

Weaning from midazolam and/or morphine was by protocol. This provides for midazolam administered by continuous infusion to be decreased by steps of 50  $\mu\text{g}/\text{kg}/\text{hr}$  per 8 hrs, and for morphine by steps of 10  $\mu\text{g}/\text{kg}/\text{hr}$  per 24 hrs.

**Measurement.** For this study we composed a checklist, which we named Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC). It contains all symptoms of benzodiazepine and opioid withdrawal described in the literature specific to critically ill children (24). The final checklist was approved by ten experienced pediatric intensivists to guarantee content validity. The 24 items of the SBOWC are listed in Table 3 (31). Tachycardia was defined as a heart rate of  $>15\%$  above the baseline value (32, 33). The latter criterion accordingly was applicable to the items tachypnea and hypertension. For heart rate, respiratory rate, and arterial blood pressure the highest values within the past 4 hrs were automatically generated by the patient data man-

agement system when the nurse completed the SBOWC. The daily baseline values for the physiologic items were also computed from patient data management system data.

All nurses of the two PICUs received verbal and written instruction on how to use the SBOWC. In addition, an instruction manual was available at each patient's bedside. Items were to be scored "yes" if the symptom had been present during the past 4 hrs. For the purpose of analysis, items assigned yes were recoded in the numeric value "1," all other items were recoded in "0." The sum score for each assessment was computed by summing the numeric values. The SBOWC sum score thus can range from 0 to 24 (no symptoms vs. all symptoms of withdrawal were observed).

**Procedure.** The attending nurse completed the SBOWC every shift at set times (4 a.m., 2 and 8 p.m.). These set times had been determined on the basis of the daily nursing staff schedule, i.e., three 8-hr shifts, taking into account that a nurse must have been able to look after the child for a minimum of 4 hrs before scoring. Scores were entered into the patient data management system, which system also "reminds" the nurse when to complete the SBOWC. For logistic reasons, data collection ceased after the child's discharge from the PICU.

**Statistical Analyses.** Descriptive statistics were used to present demographics, administered medication, and withdrawal symptoms. The doses for fentanyl were converted to morphine equivalents by the formula  $0.1 \text{ mg}/\text{kg}$  of fentanyl = 10  $\text{mg}/\text{kg}$  of morphine (34).

Spearman's rank-correlation coefficient ( $r_s$ ) was used to explore association between the variables total dose, duration of infusion, and maximum SBOWC sum score. For every  $r_s$  a 95% confidence interval (CI) was computed. The maximum sum score of the SBOWC was computed for each patient.

The observations were divided into four groups: 1) the total group, 2161 observations made in all 79 children; 2) a "weaning group," 932 observations in 76 children obtained within 24 hrs after decrease and/or discontinuation of midazolam and/or opioids; 3) a "high doses" group as a subset of the second group, 496 observation in 19 children with the highest total doses of midazolam during admission ( $>70 \text{ mg}/\text{kg}$ ) [these are children at particular risk of developing withdrawal symptoms]; 4) an "unsuccessful weaning" group, 93 observations in 27 children [these observations were obtained before increasing midazolam and/or opioids during the weaning process to counteract possible withdrawal-related symptoms].

Interobserver reliability was tested for the dichotomous items by Cohen's kappa and the intraclass-correlation coefficient for continuous data (35). A Cohen's kappa below 0.65 was considered unsatisfactory (36). SBOWC assessments were excluded for analysis when three or more ( $>10\%$ ) items were missing. A  $p$  value of  $<0.05$  indicated a statistical significance.

## RESULTS

**Patients.** During the study period, a total of 687 patients were admitted, 91 patients received prolonged midazolam and/or opioids, however, 12 patients were excluded. Of these, 10 of 12 patients were admitted with status epilepticus and treated with midazolam, and two patients had severely disturbed behavior pattern (one patient with syndrome of West and another patient with infantile encephalopathy with choreoathetosis) due to underlying neurologic disease. Thus, 79 (11%) patients fulfilled the inclusion criteria and were enrolled in this study. Median age was 3.4 months (range, 0 days–15.5 yrs). Demographic data and background characteristics are listed in Table 1.

**Medication.** Specifics of dosing and duration of medication are given in Table 2. All 79 patients were sedated with midazolam at a median dose of 176  $\mu\text{g}/\text{kg}/\text{hr}$  (range, 25–397). Seventy-three (92%) patients also received opioids. Midazolam

Table 1. Patient characteristics (n = 79)

Variables	n	%
Sex		
Male	45	57
Female	34	43
Age		
Neonate (<28 days)	19	24
1–6 mos	26	33
6–12 mos	12	15
1–3 yrs	11	14
3–10 yrs	9	11
>10 yrs	2	3
Age (mos), median (range)	3.4 (0–185)	
Diagnosis		
Respiratory insufficiency	34	43
Cardiac (pre- and postoperative after $\geq 48$ hrs)	21	27
Postoperative	9	11
Congenital defects	5	6
Sepsis	4	8
Other	6	5
Surgery (yes)	56	71
ECMO therapy (yes)	11	14
Ventilation		
No. patients	76	96
No. days <sup>a</sup>	8 (1–107)	
Length of stay	11 (7–21)	
PICU <sup>b</sup> (days)		
Pediatric Index Mortality Score <sup>a</sup> (%)	3.2 (0.4–43.7)	
Pediatric Risk of Mortality <sup>a</sup> (%)	13 (0–32)	

ECMO, extracorporeal membrane oxygenation; PICU, pediatric intensive care unit.

<sup>a</sup>Median (min–max); <sup>b</sup>median (P25–P75).

Table 2. Continuous midazolam and opioid intravenous infusion

	Midazolam	Opioids (Morphine and Fentanyl <sup>c</sup> )
No. patients	79	73
No. days <sup>a</sup>	10 (3–108)	8 (1–41)
Mean continuous doses (μg/kg/hr) <sup>a</sup>	176 (25–397)	14 (5–559)
Maximum doses (μg/kg/hr) <sup>a</sup>	300 (25–700)	20 (2–1200)
Total doses during admission (mg/kg) <sup>b</sup>	33 (2–595) [20–70]	3.8 (0–682) [1–11]

<sup>a</sup>Median (min–max); <sup>b</sup>median (min–max) and [patients 25 to 75]; <sup>c</sup>the doses for fentanyl were converted to morphine equivalents (34).

was administered for a median 10 days (range, 3–108 days). The median total dose of midazolam administered was 33 mg/kg (range, 2–595) and of opioids, 4 mg/kg (range, 0–682). Opioids were administered for a median of 8 days (range, 1–41 days).

The first-line drugs were midazolam, morphine, and fentanyl. Several patients received additional drugs such as ketamine (n = 26), propofol (n = 14), and clonidine (n = 26) to relieve distress and/or pain.

**Interobserver Reliability.** Twenty-three observations were scored simultaneously by the attending nurse and the principle investigator (EI). The intraclass-correlation coefficient was 0.85 (95% CI 0.69–0.94). The interobserver reliability (Cohen's kappa) of the individual items of the SBOWC ranged from 0.59 to 1.0. Interobserver reliability for the items high-pitched crying (0.59), and mottling (0.62) showed a kappa below 0.65.

**Withdrawal Symptoms.** A total of 2188 assessments were performed in 79 children. Twenty-seven observations in 14 patients were excluded from analysis because >2 items were missing. The median number of assessments in individual patients was 14 (range, 2–198) over a median of 6 days (1–67 days). In three patients, there were no observations performed after weaning or cessation of midazolam and/or opioids because they were discharged. The frequencies of withdrawal symptoms for the groups defined above are summarized in Table 3.

**Central Nervous System Irritability.** Symptoms such as anxiety, agitation, grimacing, sleep disturbance, increased muscle tension, and movement disorder were observed in >10% (10%–22.1%) of all observations. Their frequencies differed little between the total, weaning, and high-doses groups.

Symptoms such as seizures, tremors, high-pitched crying, pupil dilation, and

hallucinations were rarely seen (0%–4%) in all groups.

The unsuccessful weaning group showed much higher frequencies of the symptoms agitation, anxiety, increased muscle tone, motor disturbance, grimacing, and sleep <1 hr (20.4%–46.2%) than observed in the two other weaning groups. Figure 1 illustrates this finding. Administration of additional sedatives and analgesics, including ketamine, clonidine, and propofol, was slightly higher (10.5%) in the unsuccessful weaning group as compared with the total group. On the other hand, in 45 (48%) of the 93 assessments in this group midazolam, morphine, and fentanyl were tapered off before administering additional medication. Strikingly, in 13 of 45 observations the tapering rate was between 10% and 20% per step. In 32 of 45 cases these medications were tapered off faster (>20% of initial doses) indicating that tapering rate might be a factor of influence.

**Gastrointestinal Dysfunction.** Diarrhea and increased gastric residuals after feeding were most frequently observed (respectively, 14.5%–22.6% and 12.4%–25.5%) in all four groups. Vomiting was seen twice more frequently (11.8%) in the unsuccessful weaning group than in the three other groups. Frequency of increased gastric residuals after feeding was higher in this group as well.

**Autonomic Dysfunction.** Tachypnea, fever, sweating, and hypertension were observed in >13% of assessments in all four groups. Sneezing and yawning were rarely observed in all the groups. The unsuccessful weaning group showed higher frequencies of notably the symptoms sweating and mottling with a relative increase of 10% or more (see Fig. 1).

**Correlation between SBOWC Sum Scores and Doses Medication.** The maximum SBOWC sum scores per patient ranged from 1 to 12 with a median of 6.

The  $r_s$  between total doses of midazolam and maximum SBOWC sum score in

76 children was 0.51 (95% CI 0.32–0.66,  $p < 0.001$ ). The  $r_s$  between total doses of opioids and the maximum SBOWC sum score was 0.39 (95% CI 0.17–0.57,  $p < 0.01$ , n = 71). The correlation between duration of medication and maximum SBOWC sum score was 0.52 (95% CI 0.34–0.67,  $p < 0.001$ , n = 76).

## DISCUSSION

This study in a large PICU population is the first that prospectively evaluates occurrences of all 24 benzodiazepine and opioid withdrawal symptoms described in the literature for PICU patients. Previous publications included fewer symptoms or focused on either opioid or benzodiazepine withdrawal symptoms (4, 5, 7, 9).

Only Franck et al. (10) prospectively studied both benzodiazepine and opioid withdrawal symptoms. The number of symptoms was limited to 16, however, and the study group included only 15 patients with a complex congenital heart disease. Their findings demonstrate that symptoms like sleeplessness, temperature above 37.2°C, diarrhea, tremors, and pupil dilation were most frequently observed, which coincides with findings in the present study, except for tremors. Based on the literature we did not expect gastrointestinal symptoms such as diarrhea and vomiting as withdrawal symptoms in patients with midazolam (37). However, two of six patients who received only midazolam showed gastrointestinal symptoms not caused by viral infection or use of antibiotics. Still, this is no clear evidence to state that gastrointestinal symptoms can be seen as benzodiazepine withdrawal symptoms.

Several authors found correlations between withdrawal symptoms and total cumulative doses (mg/kg) of midazolam or opioids (4, 5, 7, 10, 11, 38). In this study, we found similar significant correlations. We also found correlations between duration of use and total dose of midazolam administration on the one hand, and maximum SBOWC sum score on the other hand (respectively, 0.52 and 0.51). The correlation between total doses of opioids and maximum sum score ( $r_s = 0.39$ ) is moderate.

We found that patients whose medication is tapered off (weaning group) and those with high cumulative total doses (high-doses group) were at risk for developing withdrawal symptoms during

Table 3. Frequencies of observed withdrawal symptoms

Observation Item	Total Group, (2,161 Observations in 79 Patients)		Weaning Group, (932 Observations in 76 Patients)		High-doses Group, <sup>a</sup> (496 Observations [After Decreasing Medication] in 19 Patients)		Unsuccessful Weaning Group, (93 Observation in 27 Patients)	
	n (%)	No. Patients	n (%)	No. Patients	n (%)	No. Patients	n (%)	No. Patients
Central nervous system irritability								
Agitation	440 (20.4)	57	197 (21.1)	50	110 (22.2)	17	43 (46.2)	17
Anxiety	334 (15.5)	41	139 (14.8)	35	85 (17.1)	13	23 (24.7)	11
Increased muscle tension	322 (14.9)	38	121 (13.0)	30	92 (18.5)	15	26 (28.0)	13
Motor disturbance								
Slight muscle jerks	151 (7.0)	30	65 (7.0)	21	37 (7.5)	8	8 (8.6)	5
Uncoordinated, robust movements	296 (13.8)	43	120 (12.8)	34	60 (12.1)	15	27 (29.0)	15
Tremors								
Spontaneous	42 (1.9)	9	17 (1.8)	6	17 (3.4)	6	2 (2.2)	1
In response to stimuli	23 (1.1)	11	9 (1.0)	5	4 (0.8)	2	1 (1.1)	1
Inconsolable crying	141 (6.5)	38	68 (7.3)	31	39 (7.9)	14	10 (10.8)	7
High-pitched crying	57 (2.6)	18	34 (3.6)	15	18 (3.6)	6	4 (4.3)	3
Grimacing	212 (9.8)	36	94 (10.1)	23	58 (11.7)	10	18 (19.4)	9
Sleep pattern								
Sleeps <1 hr	307 (14.3)	54	135 (14.6)	47	63 (12.7)	17	20 (21.5)	15
Sleeps >1 and <3 hrs	1262 (58.7)	73	535 (57.7)	69	310 (62.5)	19	57 (60.2)	22
Seizures	6 (0.3)	4	3 (0.3)	2	3 (0.6)	2	0	0
Pupil dilatation	30 (1.4)	14	11 (1.2)	9	8 (1.6)	6	2 (2.2)	2
Hallucinations	16 (0.7)	8	10 (1.1)	5	4 (0.8)	2	1 (1.1)	1
Gastrointestinal dysfunction								
Vomiting	102 (4.7)	21	42 (4.5)	16	27 (5.4)	8	11 (11.8)	5
Diarrhea	312 (14.5)	45	166 (17.8)	36	87 (17.5)	12	20 (21.5)	10
Increased gastric residuals after feeding	280 (13.0)	32	115 (12.4)	26	75 (15.1)	12	24 (25.5)	10
Poor feeding	34 (1.6)	9	15 (1.6)	8	9 (1.8)	4	0	
Autonomic dysfunction								
Tachycardia	168 (7.8)	53	87 (9.3)	40	42 (8.5)	13	15 (16.1)	9
Tachypnea	610 (28.3)	72	276 (29.6)	62	160 (32.3)	19	29 (31.2)	17
Hypertension <sup>b</sup>	169 <sup>c</sup> (15.0)	42	82 <sup>d</sup> (14.6)	33	35 <sup>e</sup> (13.1)	12	8 <sup>f</sup> (13.6)	6
Fever	397 (18.4)	39	164 (17.6)	28	97 (19.6)	9	23 (24.7)	10
Sweating	411 (19.0)	32	120 (12.9)	23	71 (14.3)	10	21 (22.6)	7
Sneezing	27 (1.2)	11	9 (1.0)	6	5 (1.0)	3	1 (1.1)	1
Yawning	63 (2.9)	23	18 (1.9)	12	9 (1.8)	5	4 (4.3)	4
Mottling	203 (9.4)	19	86 (9.2)	13	73 (14.7)	6	14 (15.1)	7

<sup>a</sup>Cumulative doses of midazolam  $\geq 70$  mg/kg; <sup>b</sup>Hypertension only determined in patients with arterial line; <sup>c</sup>n = 1130; <sup>d</sup>n = 560; <sup>e</sup>n = 267; <sup>f</sup>n = 58. n, number of observations scored with yes.

weaning. Surprisingly, frequencies of withdrawal symptoms hardly differed between total group and these subsets of observations, in which higher frequencies would have seemed likely. Thus, the observed symptoms need not necessarily have been withdrawal symptoms, but may have been expressions of discomfort, pain, or ventilator distress. Based on these findings and in line with other authors, we recommend awareness of possible overdiagnosis of withdrawal symptoms (25). For example, fever or vomiting should never be attributed to withdrawal until other possible causes are excluded. With other authors we agree that the occurrence of withdrawal symptoms must be time-related to a decrease or discontinuation of sedatives and analgesics (5–7, 10, 13, 14, 27, 39). Furthermore, the results of this study underscore that withdrawal symptoms are more

likely to occur in patients receiving high (cumulative) doses of midazolam and/or morphine.

Strikingly, a particular set of symptoms stood out clearly in this unsuccessful weaning group (agitation, increased muscle tension, anxiety, grimacing, sleeping <1 hr, poor feeding, and tachypnea). These symptoms therefore need to be included in an assessment tool. Of symptoms occurring less frequently, yawning and sneezing require constant observation and may therefore be difficult to assess in a reliable manner. Symptoms such as tremors, hallucinations, and seizures may have a high positive predictive value, even if seen less frequently.

Based on the findings of this study, we propose that the SBOWC could form the basis for an assessment tool for withdrawal symptoms in PICU patients. Still

we believe it is questionable if all items in the SBOWC were clinically relevant. Therefore, it is necessary to prospectively study the co-occurrences of several symptoms. In a further study, it would be advisable to have independent observers assess videotaped material, so as to increase the validity and reliability. Also, items of the checklist should be further clarified so as to ensure there is no misinterpretation possible for nurses. Item reduction would seem advisable to achieve easier clinical use. Particularly the two items for which low interobserver reliability was obtained should be investigated for their relevance. A way of dealing with these items is giving them more emphasis during training of nurses. On the other hand, it would be worthwhile to investigate if the items with a kappa below 0.65 are relevant for the final assessment tool.

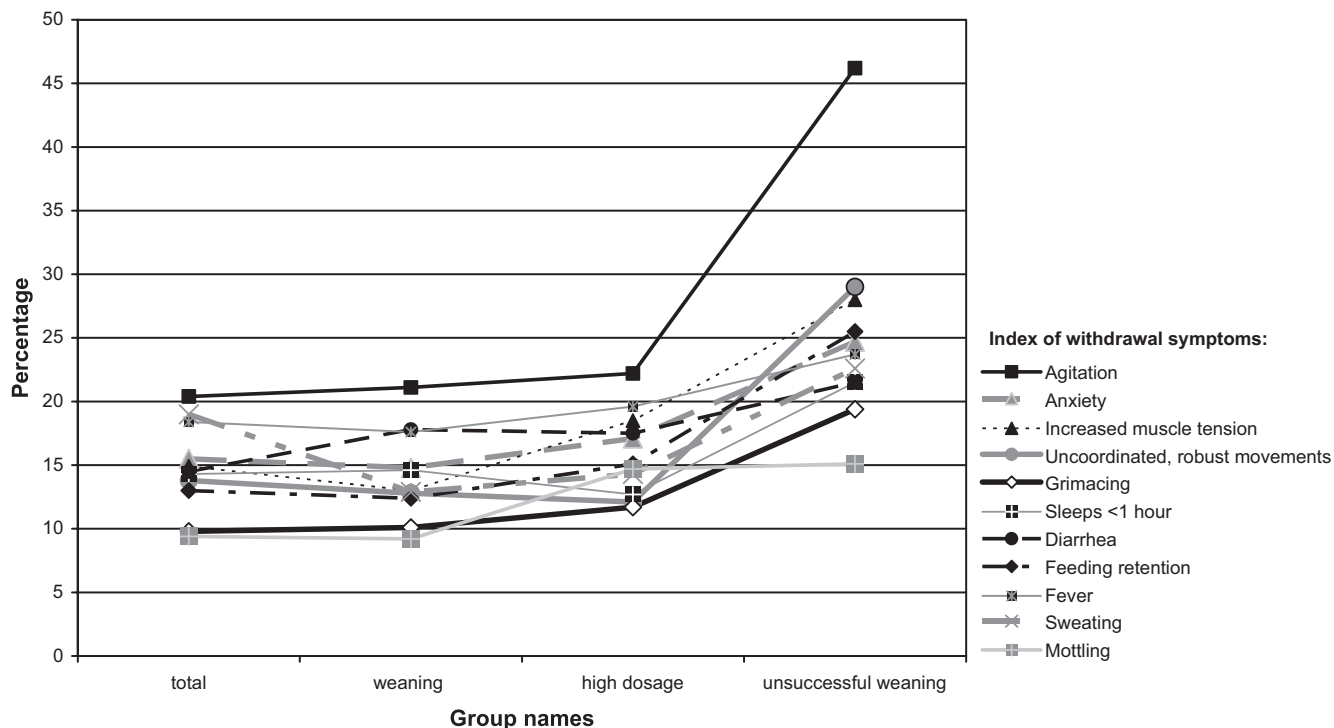


Figure 1. Frequencies (>10%) of withdrawal symptoms.

Some limitations of this study must be pointed out. First, there may have been observer bias arising from the fact that the observers were the ones who nursed the children. Second, when completing assessment forms in the patient data management system, nurses were not blinded to earlier recorded assessments. This may have influenced objectivity. Third, the frequencies of benzodiazepine and opioid withdrawal symptoms may have been influenced by administration of additional sedatives. Long-term administration of these sedatives is known to cause withdrawal symptoms as well (25, 38, 40). Fourth, the fact that weaning in this study might differ from weaning strategies in other centers might influence the prevalence of withdrawal symptoms.

For treatment purposes, opioid withdrawal symptoms need to be distinguished from those of benzodiazepines because each type of withdrawal syndrome is treated differently (24, 25). This was not possible, however, in the present study, because 73 of 79 children received both types of medication, as is common practice in PICU patients (41, 42). The subset of six patients receiving only midazolam is too small to allow conclusions on specific benzodiazepine withdrawal symptoms.

In conclusion, this is the first study which gives a complete overview of frequencies of all 24 known withdrawal symptoms after tapering off or cessation of benzodiazepines and/or opioids in PICU patients. Both longer duration of administration and higher total doses of midazolam and opioids were clearly related with the occurrence of withdrawal symptoms, and may therefore be considered risk factors.

The checklist (SBOWC) used in this study now forms the basis for a psychometric validation study aimed at establishing a clinically useful assessment tool for PICU patients who could facilitate prevention of withdrawal syndrome and application of a treatment algorithm.

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