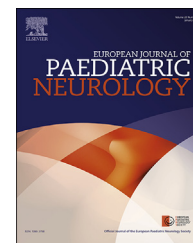




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Original article

Effect of rescue medication on seizure duration in non-institutionalized children with epilepsy



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ABSTRACT

Objectives: Characterize the real-world management of and outcomes for children with epilepsy receiving rescue medication for prolonged acute convulsive seizures (PACS) in the community.

Methods: PERFECT-3 (Practices in Emergency and Rescue medication For Epilepsy managed with Community-administered Therapy 3) was a European, retrospective observational study. Eligible patients were non-institutionalized children with epilepsy aged 3–16 years who had experienced ≥ 1 PACS in the past year and had ≥ 1 currently prescribed PACS rescue medication. Investigators provided clinical assessments and parents/guardians completed questionnaires. Statistical tests were *post hoc*; *p* values are descriptive.

Results: At enrollment ($N = 286$), most patients had prescriptions for diazepam (69.2%) and/or midazolam (55.9%); some had two (26.6%) or three (2.4%) prescribed rescue medications. Most patients experienced PACS despite regular anti-epilepsy medication. According to parents, the average duration of their child's seizures without rescue medication was < 5 min in 35.7% of patients, 5– < 20 min in 42.6%, and ≥ 20 min in 21.7% ($n = 258$); with rescue medication seizure duration was < 5 min in 69.4% of patients, 5– < 20 min in 25.6%, and ≥ 20 min in 5.0%. Rescue medication use was significantly associated with average seizures lasting < 5 min ($\chi^2 = 58.8$; $p < 0.0001$). At the time of their most recent PACS, 58.5–67.8% of children reportedly received rescue medication within 5 min of seizure onset, and 85.4–94.1% within 10 min.

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Conclusion: This study provides the first real-world data that rescue medications administered in the community reduce the duration of PACS in children with epilepsy. Study limitations including potential recall bias are acknowledged.

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1. Introduction

Most seizures experienced by children with epilepsy stop spontaneously within 5 min, but prolonged seizures lasting longer than 5 min are likely to progress to status epilepticus without treatment.¹ Convulsive status epilepticus can cause irreversible neurological damage and death (mortality about 3–5%), and requires early treatment to control seizures and improve outcomes.² Status epilepticus is conceptually defined as a seizure lasting 30 min or more, but operationally defined (for the purposes of administration of emergency treatment) as a seizure lasting 5 min or more.³ Patients may need to have their rescue medication administered to them outside of the professional healthcare environment, including at home, at school, or in other community settings. Randomized controlled studies have shown that benzodiazepine rescue medications terminate seizures when given in the emergency department⁴ or by paramedics.⁵ Despite widespread prescription for community use, there is only sparse evidence that rescue medication administered to children by parents, teachers, or other caregivers reduces seizure duration and prevents status epilepticus. Clinical guidelines offer few recommendations regarding whether and when community caregivers should administer rescue medication.⁶ The few studies of home use of rescue medication that compared treated and untreated seizures have focused on emergency hospital admissions⁷ or the frequency of acute repetitive seizures.^{8,9}

PERFECT-3 (Practices in Emergency and Rescue medication For Epilepsy with Community-administered Therapy 3) was a large-scale European study that was designed to provide real-world evidence about how prolonged acute seizures (PACS) are managed at home, at school, and in the wider community from the perspective of paediatric patients, their parents/guardians, and their physicians. Here, we characterize PACS rescue medication use and the outcome of seizure duration in children receiving rescue medication in the community. The value of this real-world information about the use of rescue medication, together with the limitations of the study, including recall bias, are discussed.

2. Methods

2.1. Design

PERFECT-3 was a European, retrospective, observational, survey-based study of the real-world management of PACS

from the perspective of patients, caregivers and physicians. Eligible patients were non-institutionalized children (aged 3–16 years) who had been diagnosed with epilepsy at least 12 months previously, had experienced one or more PACS in the past 12 months, and had one or more current prescriptions for PACS rescue medication. PACS were defined as clinically registered convulsive seizures lasting longer than 5 min. Patients with pseudoseizures, other nonepileptic events, or febrile convulsions with no diagnosis of epilepsy were excluded from the study.

2.2. Ethics and conduct

The study was conducted from July 2013 to May 2014 in accordance with the International Conference on Harmonisation of Good Clinical Practice, the Declaration of Helsinki, and local ethical and legal requirements for non-interventional studies (where applicable).

Patients were identified by consecutive sampling of eligible children attending their usual centre visits. After obtaining informed consent from parents/guardians and assent from children aged 7–16 years, physicians registered eligible patients from 20 specialist paediatric neurology centres and paediatric departments in Germany, Italy, Spain, and the UK. The planned sample size was 20 patients from each study centre; a nationally representative patient sample was sought from each participating country. The web-based system allowed enrollment of patients only if the quota for their age group (3–6 years, 7–12 years, and 13–16 years at study enrollment) in each country had not been filled.

2.3. Assessments

Demographic, medical history, and treatment information, including prescribed PACS rescue medications, were extracted from patients' medical records and entered into a web-based system by site staff. Web-based questionnaires were completed by investigators (13 questions) and parents/guardians (110 questions) to document their experience of caring for children with PACS in the community. Epilepsy aetiology responses from investigator questionnaires were classified according to the latest terminology recommended by the International League Against Epilepsy (ILAE).¹⁰ The recall period for questions in the survey was up to 12 months. In the case of missing responses, parents/guardians and investigators were prompted by email reminders through the web-based system to complete all questions. All web-based questionnaires were completed at the convenience of the parent/guardian and were available from any computer with

internet access. Access to the relevant questionnaire was obtained using a key and URL provided by the study centre. Other measures included in this study were patient/proxy questionnaires and quality-of-life instruments (results to be reported in a subsequent publication).

2.4. Data analysis

This observational study had no pre-specified primary endpoint. Analyses were performed for all enrolled patients with survey data entered into the web-based system; incomplete questionnaires were not analyzed. The duration of seizures both without rescue medication and when rescue medication was given was obtained from parents' responses to two survey questions: 'When your child experiences a prolonged seizure, on average how long does it last when no rescue medication has been given?' and 'When your child experiences a prolonged seizure, on average how long does it last after rescue medication has been given?'. Responses were based on parental recollections from the previous 12 months. The available response categories were: 0–<5 min, 5–<10 min, 10–<15 min, 15–<20 min, or ≥ 20 min. Statistical tests (χ^2) were conducted *post hoc*, and *p* values are descriptive.

3. Results

3.1. Patients

Clinical data were extracted from medical records for all 286 enrolled children (Germany, *n* = 92; Italy, *n* = 75; Spain, *n* = 77; UK, *n* = 42) (Table 1). Questionnaires were completed by investigators for 281 children and by parents/guardians for 258 children (Table 1). Enrolled patients were aged 3–16 years (median, 8) and 54.9% were boys (Table 1). According to investigator responses (*N* = 281), epilepsy aetiology was

genetic in 30.6% of patients, structural in 29.9%, other/unknown in 37.7%, and metabolic in 1.8% (Table 1). Nearly all patients (96.4%; *N* = 281) were receiving prescribed anti-epileptic medication at the time of study entry; 26.3% were receiving monotherapy, 40.2% were receiving bitherapy, and 29.9% had 3 or more anti-epileptic drugs prescribed. Prescribed anti-epileptic drugs included valproic acid (47.7%), levetiracetam (28.5%), clobazam (23.8%), lamotrigine (17.8%), topiramate (17.8%), and oxcarbazepine (13.2%), and 16.0% were receiving non-pharmacological treatment (ketogenic diet, vagus nerve stimulation, or unknown/other). Despite receiving regular anti-epilepsy medication, most patients (199/258; 77.1%) continued to experience PACS that lasted longer than 5 min and required rescue medication, according to parents.

3.2. PACS frequency

At study entry, patients had experienced 1–400 PACS in the past 12 months; 8 patients had experienced more than 200 PACS (Table 1). A skewed distribution of PACS frequency was observed in the parent survey (Fig. 1A); 44.9% of patients had experienced fewer than 2 or 3 PACS in the past 12 months, and 3.9% had experienced several PACS a day (*N* = 258). A skewed distribution of PACS frequency was also observed in medical record extracts (data not shown).

3.3. Prescribed rescue medications

Overall, 69.2% of enrolled children had prescriptions for diazepam and 55.9% for midazolam at study entry; some had two (26.6%) or three (2.4%) prescribed rescue medications (Fig. 1B) (*N* = 286). The formulation was buccal, rectal, or other for 5.1%, 77.3%, and 17.7% of the 198 diazepam prescriptions and 91.3%, 0.6%, and 7.5% of the 160 midazolam prescriptions, respectively. Other rescue medications prescribed included

Table 1 – Patient demographics, clinical characteristics, and disposition.

Characteristic	Overall (<i>N</i> = 286)	Germany (<i>n</i> = 92)	Italy (<i>n</i> = 75)	Spain (<i>n</i> = 77)	UK (<i>n</i> = 42)
Age, years					
Mean \pm SD	8.8 \pm 3.8	8.9 \pm 4.0	8.7 \pm 3.5	7.8 \pm 3.7	10.2 \pm 3.9
Median (range)	8 (3–16)	8 (3–16)	8 (3–16)	7 (3–15)	11 (3–16)
Sex, male					
<i>n</i> (%)	157 (54.9)	43 (46.7)	45 (60.0)	46 (59.7)	23 (54.8)
Time since epilepsy diagnosis, years					
Mean \pm SD	5.2 \pm 4.0	5.4 \pm 4.4	5.7 \pm 4.0	4.0 \pm 2.8	6.2 \pm 4.5
Median (range)	4 (0–16)	5 (0–16)	6 (0–15)	4 (0–12)	6 (0–15)
Number of PACS in the past 12 months					
Mean \pm SD	23.6 \pm 59.8	34.0 \pm 77.8	9.7 \pm 16.5	23.6 \pm 58.1	25.2 \pm 63.7
Median (range)	4 (1–400)	8 (1–400)	4 (1–100)	3 (1–345)	6 (1–365)
Survey completion					
Investigator, <i>n</i>	281	91	74	75	41
Parent, <i>n</i>	258	87	74	72	25
Investigator reported epilepsy aetiology					
Genetic, <i>n</i> (%)	86 (30.6)	28 (30.8)	26 (35.1)	21 (28.0)	11 (26.8)
Structural, <i>n</i> (%)	84 (29.9)	35 (38.5)	17 (23.0)	21 (28.0)	11 (26.8)
Other/unknown, <i>n</i> (%)	106 (37.7)	23 (25.3)	31 (41.9)	33 (44.0)	19 (46.3)
Metabolic, <i>n</i> (%)	5 (1.8)	5 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)

PACS = prolonged acute convulsive seizures; SD = standard deviation.

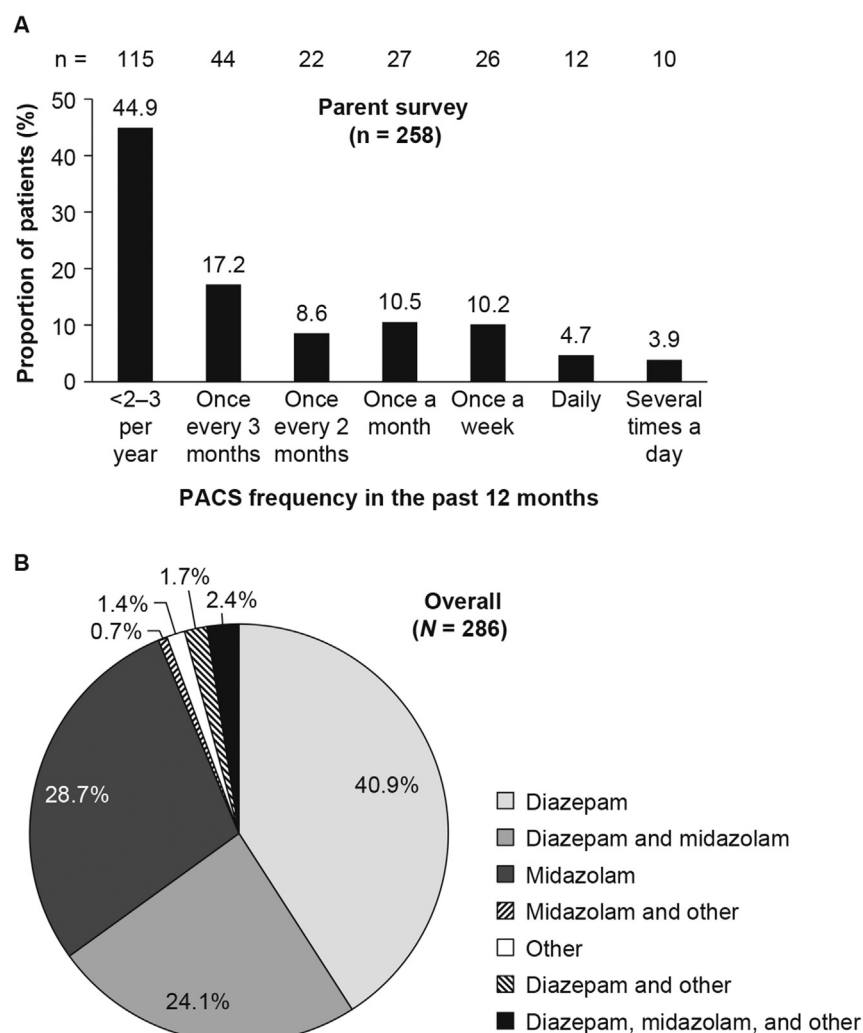


Fig. 1 – (A) PACS frequency in the past 12 months, from the parent survey; and (B) prescribed PACS rescue medication(s) at study entry, from medical records. Other rescue medications were lorazepam (10 patients), paraldehyde (1 patient), and unspecified rescue medication (7 patients). PACS = prolonged acute convulsive seizures.

lorazepam and paraldehyde. Rescue medication prescription patterns differed across countries (Fig. S.1).

3.4. Average duration of seizures with and without rescue medication

Parents of 258 of the 286 enrolled patients completed the parent questionnaire. According to parental recollections, of the 166 children whose average untreated seizures lasted 5 min or longer, 141 (84.9%) shifted to a shorter average seizure duration category when given rescue medication, and treated seizures lasted an average of less than 5 min in 91 (54.8%). Shifts in average seizure duration per child with and without rescue medication are represented in Table 2. Rescue medication was significantly associated with average seizures lasting less than 5 min, compared with seizures lasting 5 min or longer ($\chi^2 = 58.8$; $p < 0.0001$). Overall, parents reported that average seizures lasted 20 min or longer in 56/258 children (21.7%) without rescue medication and 13/258 (5.0%) when rescue medication was given (Fig. 2A). In each of the four

countries, a smaller proportion of children had seizures lasting more than 20 min and a greater proportion had seizures lasting under 5 min when they received rescue medication than when their seizures were not treated (Fig. S.2).

3.5. Administration of rescue medication in the community

Data on children's most recent PACS were available for 253 of the 258 patients in the parent survey. Parents reported that similar proportions of children received rescue medication at the time of their most recent seizure regardless of the location. Rescue medication was given at the time of the seizure to 118/171 (69.0%) of children who had their most recent PACS at home, 24/32 (75.0%) at school, and 41/50 (82.0%) elsewhere (Fig. 2B). Of these patients, 58.5–67.8% reportedly received rescue medication within 5 min of seizure onset, and 85.4–94.1% within 10 min.

As a result of the training and information they had received, 248/258 (96.1%) of parents felt at least moderately

Table 2 – Shifts in parent-reported average seizure duration category for each child with and without rescue medication.

Average duration of child's seizure, n (%)						
Without rescue medication	When rescue medication has been given					
	All, n	0 to <5 min	5 to <10 min	10 to <15 min	15 to <20 min	≥20 min
0 to <5 min	92	88 (95.7)	2 (2.2)	1 (1.1)	0 (0.0)	1 (1.1)
5 to <10 min	71	59 (83.1)	8 (11.3)	2 (2.8)	1 (1.4)	1 (1.4)
10 to <15 min	22	16 (72.7)	5 (22.7)	0 (0.0)	1 (4.5)	0 (0.0)
15 to <20 min	17	6 (35.3)	5 (29.4)	5 (29.4)	1 (5.9)	0 (0.0)
≥20 min	56	10 (17.9)	16 (28.6)	11 (19.6)	8 (14.3)	11 (19.6)
All, n	258	179	36	19	11	13

A parent of each patient was asked how long their child's seizures lasted on average, both without rescue medication and when rescue medication had been given. Available responses were: 0 to <5, 5 to <10, 10 to <15, 15 to <20, or ≥20 min. Grey background shading indicates no change in parent-reported average seizure duration category. Grey text indicates an increase and black text indicates a decrease in the parent-reported average seizure duration category when rescue medication was given compared with when it was not given.

confident about their ability to effectively administer rescue medication. Information was not collected about care plans for individual patients, including how long parents/carers had been advised to wait before administering rescue medication.

4. Discussion

This large study in four European countries provides the first real-world data that administration of rescue medication by

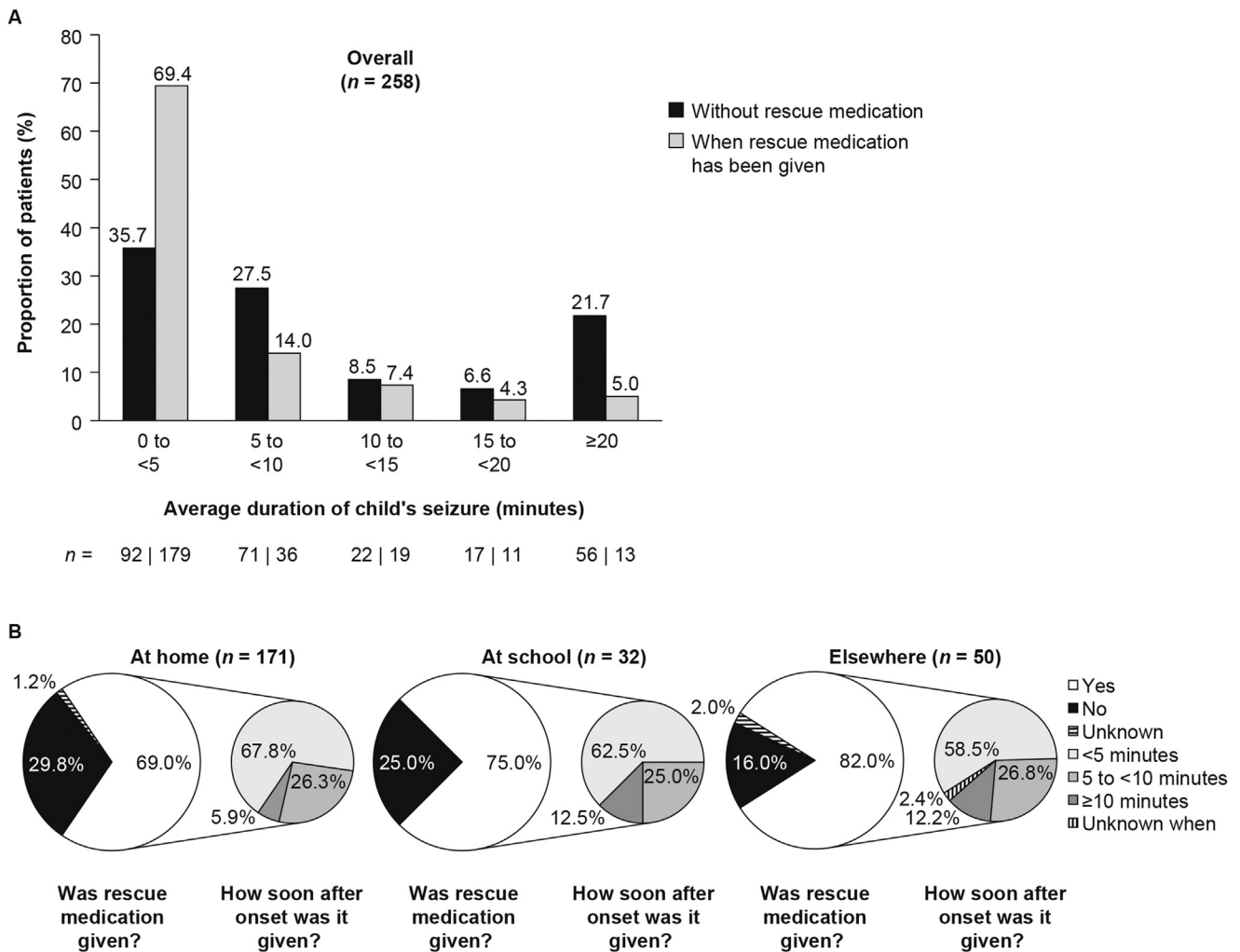


Fig. 2 – (A) Parent-reported average seizure duration for each child with and without rescue medication (overall population), and (B) rescue medication administration in the community for children's most recent seizure. Percentages are based on indicated numbers of responses to each question in the parent survey (Panel A, n = 258/258; Panel B, n = 253/258).

caregivers in the community is associated with reduced seizure duration among children with epilepsy. Participating children were non-institutionalized and most experienced PACS despite receiving regular anti-epilepsy therapy. Their prescribed rescue medications were mainly diazepam (usually rectal) and/or midazolam (usually buccal). Parents reported the average duration of their child's seizures when untreated and when rescue medication was given. Overall, more seizures lasted less than 5 min when children received their rescue medication than when they did not. Furthermore, fewer seizures lasted longer than 20 min when children received their rescue medication than when they did not.

Regardless of seizure location (home/school/elsewhere), about one-quarter of children did not receive the prescribed rescue medication for their most recent PACS, despite parents' reports that most of the children's average seizures were shorter when rescue medication was given than when they were untreated. Furthermore, about one-third of children who received rescue medication did not receive it within 5 min and about one-tenth did not receive it within 10 min for their most recent PACS. Data were not collected about why rescue medication was not given, or was given only after a certain amount of time. We speculate that the underlying reasons may have been concerns about the safety, tolerability, ease of administration, and social acceptability of the prescribed rescue medication. A lack of caregiver knowledge on patients' treatment plans, including the recommended time before administration of rescue medication after the onset of a seizure, may also explain why rescue medication was not administered at all or was not administered within a specific time interval for particular seizures. It should also be noted that parental recollections represented their perception of an 'average seizure'. Therefore, data about specific rescue medication for each individual seizure were not collected. Nevertheless, the findings suggest that improved education of parents, school staff, and other caregivers about the importance of early treatment according to the physician's recommendations could benefit children who experience PACS, in all countries and for all rescue medications. This highlights the need for clear and consistent clinical guidelines on community use of PACS rescue medication.⁶

The strengths of this study include the large European population and the collection of real-world data on non-institutionalized children with epilepsy whose PACS are managed by caregivers in the community. However, the limitations of this retrospective observational study should be taken into consideration. The study sites were generally specialized neurology centres, which may treat patients with more severe or frequent seizures than non-specialist paediatric centres, so the results may not be applicable to general clinical practice. To limit selection bias, the recruitment process involved consecutive sampling of eligible patients attending their routine centre visit. Gender effects were not investigated in this study, although each country enrolled approximately even numbers of males and females. Eligible patients were required to have had at least one PACS in the 12 months before enrollment, meaning that the study population represented a subset of children with epilepsy. However, the

selection criteria allowed recruitment of children with widely ranging disease severity (1–400 PACS/year), reflecting diversity in epilepsy aetiology and clinical practice. Limitations of the study design prevent further analysis of the disease types included in the study population. *Post hoc* stratification of results by PACS frequency may provide additional insights into the impact of PACS on patients, caregivers, and health-care services (to be reported elsewhere).

Parent responses may have been subject to recall bias because the web-based questionnaires relied on recollection of events that could have occurred in the respondents' absence and up to 12 months previously. The retrospective, non-interventional design of the study meant that seizure duration was assessed using parental perceptions of past treated and untreated seizures for each child, rather than prospective measurements in groups of patients. The survey questions did not prompt parents to enter a value, but rather to select one of five categories (0–<5, 5–<10, 10–<15, 15–<20, or ≥20 min) for the duration of each child's seizures on average, both with and without rescue medication. Asking parents or other community caregivers to record the duration of children's seizures as they occur may present ethical and practical problems, given that their priorities are to care for and monitor the child, and to administer rescue medication and seek emergency medical attention if appropriate. The possibilities of recall bias or estimation of seizure duration were not eliminated in a study comparing home use of rectal diazepam and intranasal midazolam using parent timings of seizure duration.¹¹ Finally, this non-interventional study was not designed to collect safety data or to allow comparison of specific drug therapies or routes of administration in terms of their side effects, efficacy, ease of administration, or social acceptability. Owing to differences in healthcare service providers and reimbursement models, the country of recruitment presents a confounding variable for *post hoc* comparisons of rescue medications. For example, midazolam use was highest in the UK and diazepam use highest in Spain and Italy, likely reflecting that midazolam was available through the UK NHS at the time of the study. Despite these limitations, the overall findings are relevant when considering the optimal management of children who experience PACS, including training of community caregivers to prevent status epilepticus, avoid hospitalization, and reduce the risk of long-term neurological damage.

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Potential conflict of interest

The following authors have received compensation for serving as consultants or speakers for, or they or the institutions they work for have received research support or royalties from, the companies or organizations indicated: F. Vigevano (Cyberonics, Eisai, Shire, and ViroPharma), F.J. Kirkham (Cyberonics, Eisai, Shire, and ViroPharma), B. Wilken (Shire and ViroPharma), M. Raspall-Chaure (Shire and ViroPharma), and L. Lagae (Cyberonics, Eisai, Shire, UCB, and Zogenix). R. Grebla was an employee of Shire at the time of the study and T. Werner-Kiechle is a current employee of Shire; both own stock and/or stock options. D. Lee is an employee of BresMed Health Solutions.

Contributors' statements

Dr Vigevano contributed to study concept and design, as well as acquisition, analysis, and interpretation of the data, and study supervision and coordination; Dr Kirkham, Dr Wilken and Dr Raspall-Chaure were involved in acquisition, analysis, interpretation of data, as well as study supervision and coordination; Ms Lee performed statistical analyses and contributed to study concept and design, as well as analysis and interpretation of the data; Dr Grebla and Dr Werner-Kiechle contributed to analysis and interpretation of the data; Dr Lagae contributed to study concept and design, as well as analysis and interpretation of the data; and all authors revised the manuscript for content and approved the final manuscript as submitted.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejpn.2017.07.017>.

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