Uncovering the value of autonomic signs and seizure detection in epilepsy care

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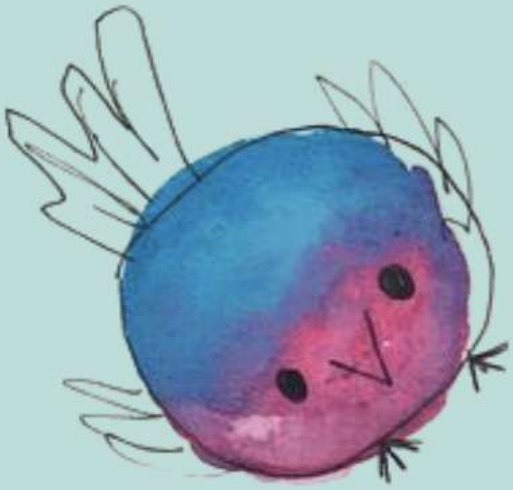

CHAPTER 5

Multimodal nocturnal seizure detection in children with epilepsy: a prospective, multicenter, long-term, in-home trial

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ABSTRACT

Introduction

There is a pressing need for reliable automated seizure detection in epilepsy care. Performance evidence on ambulatory non-electroencephalographybased seizure detection devices is low, and evidence on their effect on stress, sleep, and quality of life (QoL) is still lacking. We aimed to determine the performance of NightWatch, a wearable nocturnal seizure detection device, in children with epilepsy in the family home setting and to assess its impact on caregiver burden.

Methods

We conducted a phase 4, multicenter, prospective, video-controlled, in-home NightWatch implementation study (NCT03909984). We included children aged 4-16 years, with ≥1 weekly nocturnal major motor seizure, living at home. We compared a 2-month baseline period with a 2-month NightWatch intervention. The primary outcome was the detection performance of NightWatch for major motor seizures (focal to bilateral or generalized tonic-clonic [TC] seizures, focal to bilateral or generalized tonic seizures lasting >30 s, hyperkinetic seizures, and a remainder category of focal to bilateral or generalized clonic seizures and "TC-like" seizures). Secondary outcomes included caregivers' stress (Caregiver Strain Index [CSI]), sleep (Pittsburgh Quality of Sleep Index), and QoL (EuroQol five-dimension five-level scale).

Results

We included 53 children (55% male, mean age=9.7±3.6 years, 68% learning disability) and analyzed 2310 nights (28173h), including 552 major motor seizures. Nineteen participants did not experience any episode of interest during the trial. The median detection sensitivity per participant was 100% (range=46%-100%), and the median individual false alarm rate was .04 per hour (range=0–.53). Caregiver's stress decreased significantly (mean total CSI score=8.0 vs. 7.1, p=.032), whereas caregiver's sleep and QoL did not change significantly during the trial.

Conclusions

The NightWatch system demonstrated high sensitivity for detecting nocturnal major motor seizures in children in a family home setting and reduced caregiver stress.

INTRODUCTION

There is a pressing need for reliable automated seizure detection in epilepsy care.[1,2] Seizures are unpredictable and may cause life-threatening situations through injury, status epilepticus, and sudden unexpected death in epilepsy.[3] Convulsive seizures (i.e., focal to bilateral or generalized tonic-clonic seizures) have the highest mortality risk, particularly among those with nocturnal convulsions sleeping alone.[4-6] This suggests that having someone providing essential support following a convulsion can be lifesaving. Seizure detection devices (SDDs) are developed to alert caregivers in case of potentially dangerous seizures. This enables timely intervention, which may help reduce seizure-related risks.[3,5,7] Accurate detection may also empower people with epilepsy, by allowing them to sleep alone and relieving the burden of seizure vigilance for their caregivers.[4,8,9] Evidence on the effect of an SDD on caregiver's stress, sleep, and quality of life (QoL), however, is still lacking.[8] SDDs also have the potential to improve seizure documentation, as seizure diaries are known to be unreliable.[10] Various ambulatory non-electroencephalography (EEG)-based SDDs are available, but their performance evidence is low.[1,11] Many devices lack external validation. Almost all SDD studies were performed in a clinical setting with short follow-ups and lacking essential user feedback.[11-13] Long-term, home-based trials addressing aspects related to usability (classified as phase 4 by recent guidelines) are therefore mandatory to guide SDD implementation.[12] In a prospective phase 4 study, we demonstrated the good performance of a wearable multimodal device (NightWatch) for the detection of nocturnal major motor seizures (median sensitivity of 86% per person and median false alarm rate [FAR] of .25 per night).[14] Subsequent validation of NightWatch in a pediatric cohort revealed higher FARs, with rates amounting to .2 per hour.[15] To improve performance, we adapted the algorithm and found that it could reduce FAR to levels close to that of adults while maintaining high sensitivity.[15] We, therefore, set up a long-term, home-based phase 4 study to prospectively validate the performance of the adjusted NightWatch algorithm in children with severe epilepsy while monitoring the effect on caregiver's stress, sleep, and QoL.

METHODS

Protocol Approvals, Registrations, and Patient Consents

We conducted a multicenter, prospective, long-term, inhome implementation study (the PROMISE trial, short for Promoting the Implementation of SDDs in Epilepsy Care). We collected data between August 2018 and August 2020. The trial was registered at Clinicaltrials.gov (identifier: NCT03909984) and approved by the research ethics committee of University Medical Center Utrecht in the Netherlands (NL62995.041.17). The child's legal representatives provided written informed consent (in most cases, both biological parents) as did participants ≥12 years old when capable.

Participants

We recruited children with epilepsy aged 4-16 years from three tertiary epilepsy centers in the Netherlands, namely, Stichting Epilepsie Instellingen Nederland (SEIN), University Medical Center Utrecht (UMCU), and Academic Center for Epileptology Kempenhaeghe (KH), with at least one weekly nocturnal major motor seizure event, and living at home. Seizure frequency was based on clinical history and checked with the caregivers before signing informed consent and again before the start of the intervention. We excluded children with comorbid conditions that could lead to high false alarm rates, such as movement disorders, cardiac arrhythmias, or wearing a pacemaker. We originally defined skin pigmentation as an exclusion criterion, as we assumed that the light-based plethysmography (PPG) signal would be less reliable through pigmented skin. After validating NightWatch on pigmented skin, we discovered that the PPG method worked reliably on all types of skin pigmentation, so we abandoned this criterion after 42 inclusions.

Seizure detection algorithm

The multimodal algorithm of NightWatch, based on photoplethysmography and accelerometry (ACC) data, is described in more detail in previous publications.[14,15] Heart rate (HR) values are determined and updated every second based on a 5-min average of past individual peak-to-peak intervals. The accelerometry sensor measures motion and position, where position represents the angle of the sensor with respect to the gravity vector. Rhythmic movements are identified by counting the number of zero crossings for each axis per second. The plethysmographic waveform is evaluated to estimate the signal

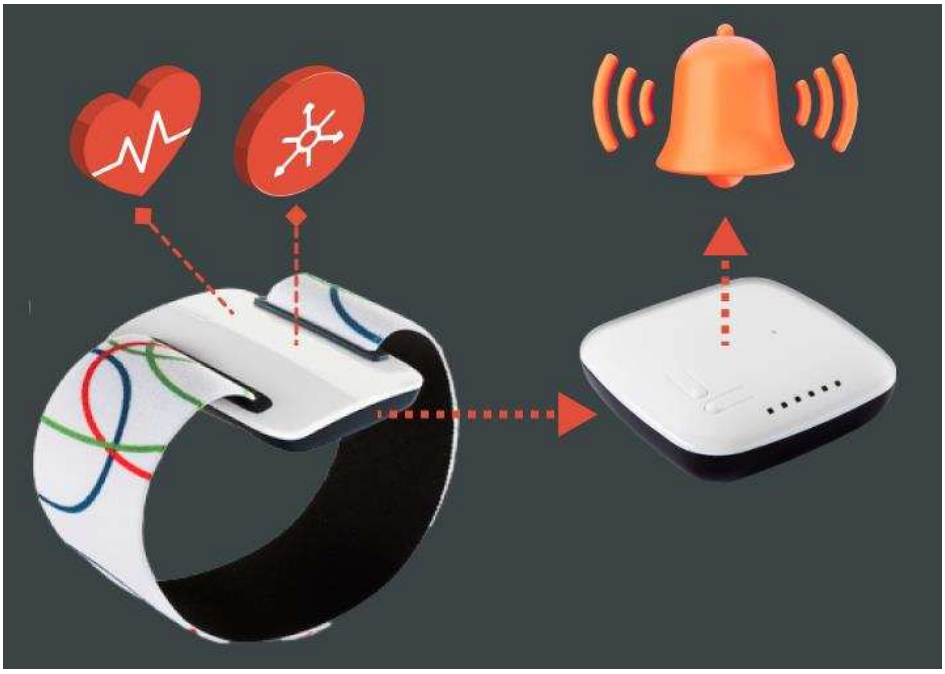

Figure 1 The **NightWatch** bracelet contains a photoplethysmographic heart rate module and a three-dimensional accelerometer. When a specific heart rate or movement threshold or pattern is detected, the algorithm triggers an alarm so caregivers can intervene. The signals or alarms are transmitted by Digital Enhanced Cordless Telecommunications Ultra Low Energy (DECT ULE) directly to the base, which may be connected to a local area network for further transmission of the data and alarms. DECT ULE is a wireless communication standard with greater range, reliability, and safety than Bluetooth or Wifi. *Figure published with permission from LivAssured.*

quality, and the multimodal algorithm is applied if the signal quality is adequate (>80%). If HR is unreliable, then only the ACC algorithm is used for detection. When both modalities are active, they work in parallel. Several situations may trigger an alarm: increasing HR slope when it exceeds an absolute or relative threshold (compared to baseline), and sustained rhythmic movements. We applied the adjusted algorithm developed in the previous pediatric trial.[15]

Intervention

The intervention consisted of a 2-month baseline period without any SDD (usual care) followed by 2months of NightWatch usage at home (intervention; Figure 1). The NightWatch base station (generating alarms) was installed in the participant's home, with a video camera and audio sensor attached to a pole

and directed to the child's bed. Data were generated only during the time NightWatch was worn. We asked participants to wear the NightWatch every night during the intervention period. All data were transmitted to a laptop in the child's room and stored for analysis. We asked the caregivers to keep a seizure diary during the intervention. After the intervention, caregivers, if they wanted to continue using the device, could purchase NightWatch for €750 (half of the regular price).

Study outcomes

The primary outcome measure was the individual performance of NightWatch to detect major motor seizures, including sensitivity, positive predictive value (PPV), F1 performance score, and FAR per hour. Secondary outcomes included the quality of the signal data, the impact of NightWatch on caregivers' stress, sleep, and QoL, and their expectations and experiences with NightWatch.

Questionnaires

We used validated questionnaires to examine caregivers' stress (Caregiver Strain Index [CSI]), sleep (Pittsburgh Quality of Sleep Index [PQSI]), and QoL (EuroQol five-dimension five-level scale [EQ-5D-5L]) during the baseline period and following the intervention. We asked one caregiver per participant to complete the online questionnaires at the start of the study (T0), after the baseline period (T1), and after NightWatch usage (T2; Figure 2). The CSI includes 13 items assessing the burden of care/stress, each carrying 1 point, with a score of 7 indicating a high-stress level. The PQSI consists of seven components, each with a range of 0-3 points, to assess sleep quality, with a global PSQI score varying from 0 (no difficulty sleeping) to 21 (severe difficulties sleeping). The first part of the EQ-5D-5L combines five dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be scored on five levels ranging from "no problems" to "extreme problems." In the second part, respondents must indicate how good or bad their health is at the given moment on a scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Additionally, we developed a questionnaire with eight items assessing caregiver's expectations and 11 items on experiences with NightWatch using a 5-point Likert scale.

Sample size

We estimated a sample size of 384 major motor seizures to obtain acceptable confidence limits (precision=4%) assuming a conservative sensitivity of 80%.[15]

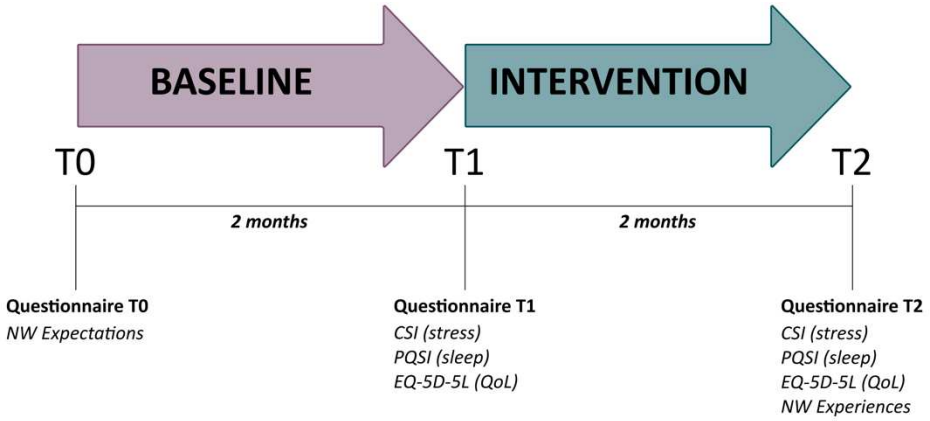

Figure 2 Study flow including a 2-month baseline period with usual care followed by a 2-month intervention period with NightWatch at home, and the different questionnaires at study points T0, T1 and T2.
CSI caregiver strain index*, EQ-5D-5L* quality of life questionnaire*, NW* NightWatch*, PQSI* Pittsburgh Quality of Sleep Index*.*

We aimed to include 60 participants with ≥1 major nocturnal motor seizure per week. We expected a 2-month intervention period (9weeks) with a dropout rate <25% to yield at least 405 significant seizures.

Data analysis

Data selection

Only full night recordings with complete and sufficient video data were included to analyze the sensor performance. Records were excluded when >75% of data transmission from NightWatch to the base station was lost, when computer storage issues had appeared, or when the nightly average signal quality of the HR measurements was <75%. The first two situations impeded the analysis of trial data but did not impact NightWatch performance at home. Poor quality of the HR data (e.g., if the sensor is not worn correctly) could potentially affect performance. The device itself constantly monitors the quality of the HR signal. If the HR data quality is insufficient for seizure detection, the NightWatch generates a distinct “technical” alarm to alert the caregiver to reposition the sensor.

Annotation process

Although video-EEG monitoring is considered the gold standard for diagnosing epileptic seizures, implementing continuous EEG was not feasible in this long-term homebased trial. We therefore made a pragmatic choice to apply video

recordings without EEG as our reference standard, focusing on motor signs for epilepsy classification. Video images were annotated with a specifically developed computer program. Trained trial nurses screened the video of 5% ofall nights for missed seizures; every video was screened by one nurse. We also retrospectively analyzed video tracings with a previously validated automated video-based seizure detection algorithm.[16-18] Trial nurses annotated all events (generated NightWatch alarms, video alarms, and caregivers' seizure diary) using the video recordings while blinded for alarm type and NightWatch sensor data (HR and movement). We considered the following seizure types as clinically urgent and classified them as "major motor seizures": (1) generalized or focal to bilateral onset tonic-clonic seizures (TCs); (2) focal to bilateral or generalized onset tonic seizures lasting >30s (T>30); (3) focal onset hyperkinetic (HK) seizures; and (4) a remainder category of other major (OM) motor seizures. Category 4 includes focal onset clonic, generalized onset, and "TC-like" seizures, the latter defined as bilateral movements without classical TC pattern (i.e., no tonic phase, pronounced asymmetry, short duration, or quick recovery). All other seizures that did not meet these criteria were classified as "non-major motor seizures" and, if detected, as false positives. In case of discrepancies (when the recorded night was annotated by one nurse, but screened by another) or doubt, the trial nurses consulted one of the principal investigators (R.D.T., R.H.C.L.) for a final decision. The principal investigators double-checked a random sample of 5% of the annotations. An event was considered true positive when an alarm was generated within 3min before or 3min after the annotated start of a seizure of interest. Other detections within a 3-min interval were scored as one event; this rule was applied for true and false positives.

Performance

We estimated performance (sensitivity, PPV, FAR, F1) per subject and the median individual performance on the population level. We excluded participants who did not have seizures of interest during the intervention period from the sensitivity, F1, and PPV analysis, but included these cases in the FAR analysis. The following formula estimated the F1 score for detection performance accuracy: F1 score=2 * (PPV×sensitivity) / (PPV+sensitivity). We performed post hoc analyses to identify clinical determinants of NightWatch performance, including age, sex, presence of learning disability, and distribution of seizure types (% TCs of the total amount of major motor seizures).

Statistics

Data are presented as mean±SD or median and range where appropriate. We used paired t-tests to analyze differences between secondary study outcomes at T1 and T2, and Mann-Whitney U-tests (sex, presence of learning disability),and Spearman rank correlation (age, % TCs) to identify clinical determinants of NightWatch performance.

RESULTS

We identified 85 eligible children, and 60 caregivers consented to participate in the trial. Seven withdrew before the intervention started due to personal situations (n=4) or seizure freedom (n=3). Of the remaining 53 participants (38 from SEIN, 10 from UMCU, and five from KH) who completed the intervention,two were excluded from the performance analysis due to lack of video recordings or recordings of insufficient video quality (e.g., wrong position

Table 1 Summary of participants' demographics

Demographic data (n=53)	No.	Mean	Range
Sex			
Male	29 (55%)		
Female	24 (45%)		
Age (years)		9.7 ± 3.6	4-16
Learning disability			
Yes	36 (68%)		
No	17 (32%)		
Epilepsy etiology			
Structural	13 (25%)		
Genetic	20 (38%)		
Infectious	1 (1%)		
Metabolic	0 (0%)		
Immune	0 (0%)		
Unknown	19 (36%)		
Epilepsy treatment			
ASMs, *n*		2.5 ± 1.2	0-6
Ketogenic diet	6		
VNS	2		

ASM Anti-seizure medication, *VNS* vagal nerve stimulation.

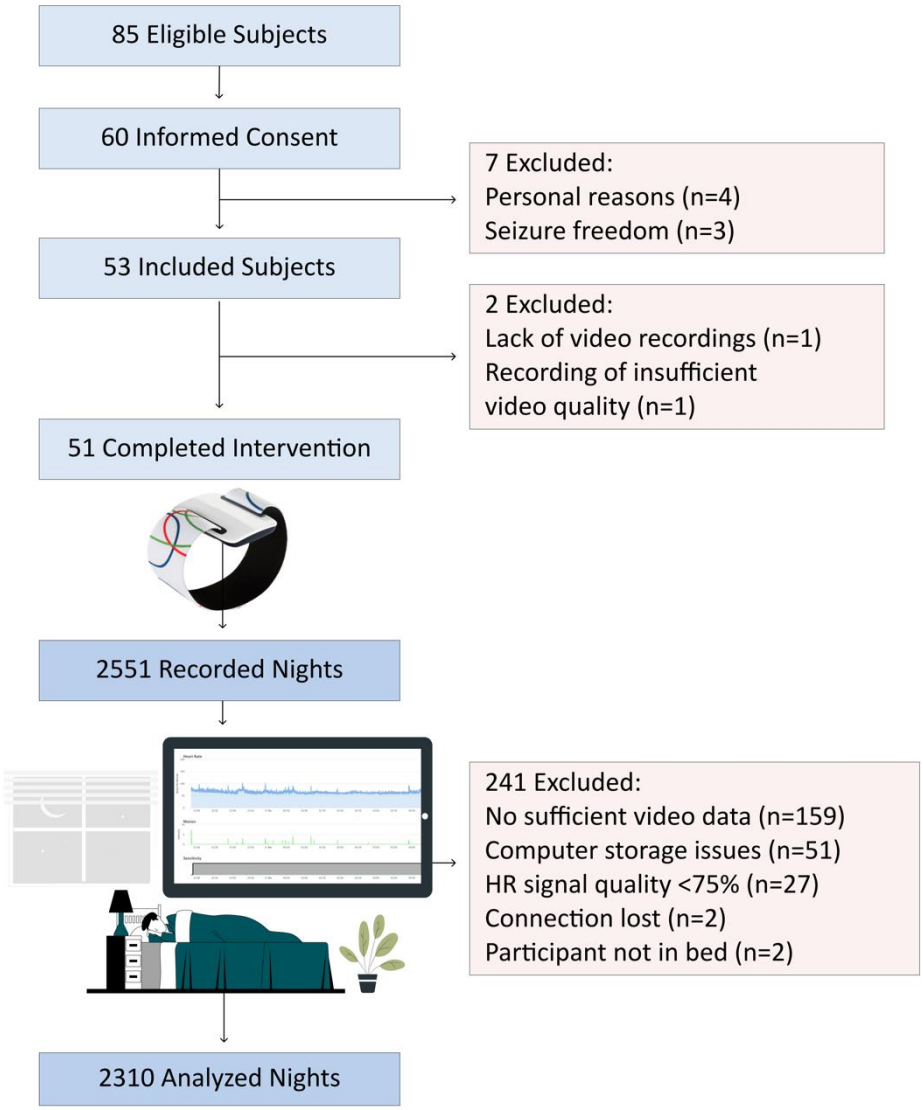

Figure 3 Study and data flow diagram. Overview of eligible subjects, included and excluded participants and selected data with reasons for exclusion.
HR heart rate.

of the camera; Figure 3). Table 1 presents the demographics of the 53 children (55% male, mean age=9.7±3.6 years, 68% learning disability). The questionnaires were completed by 51 biological parents and two legal representatives. We analyzed 2310 nights (28 173h of data, median=611h per participant [range=26-1298h]), including 552 major motor seizures (median

number of seizures per participant=2 [range=0-147]). In total, 1402h (5%) of all recorded nights were screened, ranging from half a night to four full nights per participant. All participants had a history of at least one nocturnal major motor seizure per week upon inclusion, but 19 did not have such a seizure during the intervention period. We noted medication adjustments in 18 children, resulting in higher doses of antiseizure medication in 15 children and lower doses in three.

Primary outcome: NightWatch performance

Four hundred ninety-two of 552 major motor seizures were correctly detected by NightWatch (overall seizure sensitivity=89%). Median sensitivity per participant for the detection of major motor seizures was 100% (range=46%-100%, mean=90% [95% confidence interval (CI) =84%-95%]; Table 2). We found 204 TC (37%), 30T>30 (5%), 48 HK (9%), and 270 OM (49%) seizures during the intervention. NightWatch performance for these different major motor seizure types was (median sensitivity per participant [range], overall seizure sensitivity): TC (100% [71%-100%], 94%), T>30 (100% [0%-100%], 53%), HK (75% [0%-100%], 83%), OM (100% [0%-100%], 91%; Figure 4). The median false negative alarm rate for NightWatch per participant per hour, representing the seizures missed, was 0 (range = .00-.04, mean = .002 [95% CI = .0001-.005]). NightWatch missed 60 episodes (25 OM, 14T>30, 13 TC, eight HK). These seizures were identified by the video algorithm (n=40, 67%), screening (n=13, 22%), or the caregiver (n=10, 17%). The video algorithm and the caregivers detected three missed seizures together. We identified 1642 false alarms, including 469 nonmajor motor seizures (29%). Median FAR per subject per hour amounted to .04 (range = .00-.53, mean = .07 [95% CI = .04-.10]). Median PPV per participant was 24% (range=3%-94%, mean=31% [95% CI=23%-40%]). The overall F1 score amounted to .47, with a median score of .38 per participant (range = .05-.97). We analyzed the determinants for true positive and false positive alarms. Because multiple causes can trigger one alarm, the sum of the individual numbers and percentages is more than the total amount. Of the 492 true positive alarms, 424 (86%) were triggered by accelerometry, 114 (23%) by rapid HR increase, and 90 (18%) by tachycardia. The false positive alarms were also mainly triggered by accelerometry (n=1086, 66%), followed by rapid HR increase (n=592, 36%) and tachycardia (n=103, 6%). A minority of alarms (27% of true positive and 8% of false positive alarms) were triggered by more than one signal.

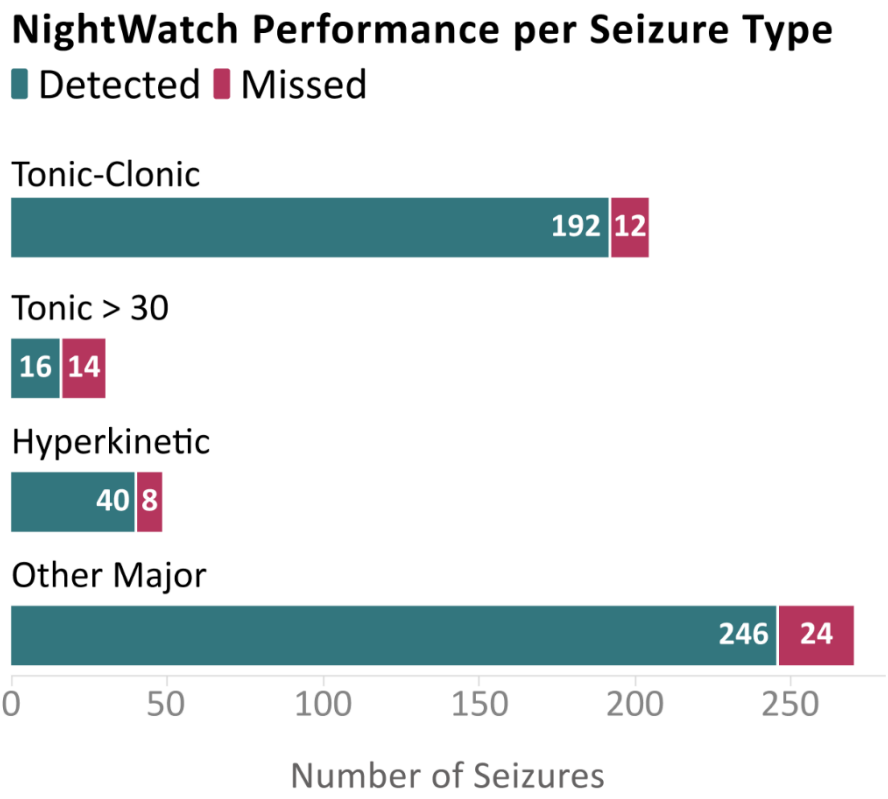

Figure 4 NightWatch performance per seizure type. Overview of number of seizures correctly detected (green bars) and number of seizures missed (red bars) by NightWatch for the different seizure types.

Post hoc analyses

Our post hoc analyses revealed that children with learning disabilities were more like to exhibit higher FAR (.05/h) than those without (.02/h, p=.001), whereas we found no contrasts in sensitivity between both groups. The other factors (age, sex, proportion of TCs) did not impact NightWatch performance.

Secondary outcomes

Quality of signal data

Two hundred forty-one of 2551 recorded nights were excluded from analysis due to insufficient video data (n=159), computer storage issues (n=51), inadequate HR signal quality (n=27), lost connection with the base station (n=2), or because the child was no longer in bed (n=2; Figure 3). In the 27 excluded

nights because of poor HR data, caregivers did not respond to the technical alarm to reposition the sensor. No data loss due to insufficient HR data was seen in cases in which NightWatch was used correctly. The accelerometry sensor provided sufficient quality signal throughout the entire study.

Adverse effects

Eight children developed mild, reversible skin irritation during the first trial period from the NightWatch device. We advised alternating recording sites (e.g., left and right arm), and in three cases we advised wearing the NightWatch around the lower leg because of skin irritation on both arms. The manufacturer developed a laser-cut kinesiology tape to stick on the inner side of NightWatch to soften skin contact. With the use of the tape, no further skin irritation was reported.

Video detection algorithm

The video detection algorithm was initially designed to detect convulsive seizures and showed a median sensitivity of 44% (range=0%-100%, mean=42% [95% CI=25%-59%]) for this type of seizure. For the detection of all major motor seizures, the median sensitivity per participant was 30% (range=0%-100%, mean=29% [95% CI=19%-39%]), with a median FAR per hour of .05 (range = .00-1.44, mean = .13 [95% CI = .06-.20]). We performed a post hoc investigation to understand why scores were lower than previously reported[16,17] and noticed that the video recordings had an unstable frame rate, which may hinder the performance of the detection algorithm. In a prospective setting this problem would never emerge, but during retrospective analysis we discovered that it is very important that the video recordings are stored with a fixed frame rate, because the algorithm has to detect specific frequencies in movement. An unstable frame rate disrupts these frequencies and thereby influences the algorithm's performance.

Questionnaires

The online questionnaires on caregiver's stress, sleep quality, and QoL were fully completed by 25 (47%) and partly completed by 17 (32%) caregivers, and the questionnaires on caregiver's expectations and experiences were fully completed by respectively 25 (47%) and 22 (42%) caregivers.

Caregiver's stress, sleep, and QoL

The mean CSI score was >7 points throughout the study, indicating high levels of caregiver stress. During the intervention period there was a small but significant decrease in caregiver stress (mean total CSI score=8.0 vs. 7.1, p=.032). The median difference in stress score was −1, and nine caregivers

Table 2 Characteristics of included subjects and individual results

Sub-ject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
1	F	8	Genetic	No	3	63	9	HK	100	69	0.01	11	9	9	3	0.74	0.80
2	M	7	Structural	No	3	43	0	-	-	-	0.01	4	2	4	2	1	1
3	F	14	Unknown	No	2	62	0	-	-	-	0.02	4	4	6	6	1	1
4	M	15	Unknown	Yes	3	38	4	TC	100	21	0.03	11	10	10	13	0.86	0.77
5	F	8	Structural	Yes	3	61	4	TC, T>30	100	11	0.04	4	na	8	na	0.90	na
6	F	6	Unknown	No	2	65	0	-	-	-	0.02	5	2	7	8	0.82	0.91
7	M	16	Genetic	Yes	2	51	2	HK, OM	50	17	0.01	1	1	2	3	1	1
8	M	9	Structural	Yes	3	30	0	-	-	-	0.17	9	7	5	8	1	1
9	M	14	Unknown	Yes	5	14	13	TC, T>30, OM	46	35	0.06	12	12	11	6	0.87	0.87
10	M	14	Genetic	Yes	2	56	147	TC, T>30, HK, OM	80	75	0.05	10	8	14	12	0.84	0.86
11	F	15	Genetic	Yes	2	14	5	HK, OM	80	29	0.06	na	na	na	na	na	na
12	M	6	Genetic	Yes	4	60	22	TC, T>30, OM	100	37	0.05	12	12	8	8	0.89	0.89
13	F	13	Structural	Yes	3	70	0	-	-	-	0	na	na	na	na	na	na
14	F	10	Structural	Yes	1	56	24	TC, T>30, OM	100	49	0.03	8	7	8	4	0.61	0.92
15	M	5	Unknown	Yes	1	Excl[b]	-	-	-	-	-	12	11	9	10	1	0.93
16	F	12	Genetic	Yes	3	25	0	-	-	-	0.19	5	7	10	11	0.91	0.93
17	M	11	Structural	No	2	32	7	OM	86	15	0.11	7	9	8	7	na	na
18	F	16	Genetic	Yes	1	18	0	-	-	-	0.53	4	6	6	4	1	1
19	M	10	Genetic	No	3	59	0	-	-	-	0.05	na	na	na	na	na	na
20	F	5	Genetic	Yes	2	81	3	OM	100	4	0.06	na	na	na	na	na	na
21	F	12	Unknown	Yes	2	20	0	-	-	-	0	na	na	na	na	na	na

Table 2 (Continued)

Subject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
22	F	15	Genetic	Yes	4	56	6	TC, T>30, OM	100	13	0.06	5	5	8	9	0.83	0.96
23	F	13	Unknown	Yes	3	45	17	TC, HK, OM	94	17	0.14	12	9	11	13	0.75	0.65
24	F	15	Unknown	No	2	31	17	HK	100	94	0	na	na	na	na	na	na
25	F	10	Genetic	Yes	2	41	10	TC, OM	100	36	0.03	10	na	4	na	0.85	na
26	M	4	Genetic	No	2	30	1	OM	100	9	0.02	9	8	0	4	na	na
27	M	8	Genetic	Yes	6	16	0	-	-	-	0.25	na	na	na	na	na	na
28	M	9	Genetic	Yes	4	57	86	OM	99	26	0.34	8	9	8	8	1	1
29	M	12	Structural	Yes	3	54	70	TC, T>30, HK, OM	87	75	0.03	9	11	7	6	0.9	0.83
30	M	4	Genetic	Yes	3	80	0	-	-	-	0.18	11	na	10	na	1	na
31	F	7	Genetic	Yes	1	54	1	TC	100	3	0.05	9	9	10	7	0.93	0.83
32	M	14	Unknown	Yes	0	16	6	TC, T>30	83	10	0.24	10	9	10	4	1	1
33	M	10	Unknown	No	2	30	4	TC, OM	100	24	0.02	na	na	na	na	na	na
34	F	8	Genetic	Yes	2	27	12	TC, T>30, OM	100	23	0.11	na	na	11	na	na	na
35	M	13	Unknown	No	2	18	0	-	-	-	0.01	na	na	na	na	na	na
36	M	8	Structural	No	2	2	2	TC	100	67	0.04	8	na	5	na	1	na
37	M	14	Unknown	Yes	3	59	35	TC, OM	100	51	0.04	9	5	4	5	1	1
38	M	5	Infectious	Yes	2	Excl.[b]	-	-	-	-	-	na	na	na	na	na	na
39	F	5	Structural	Yes	5	59	0	-	-	-	0.02	10	9	7	2	0.93	0.93
40	F	12	Unknown	No	3	57	2	T>30, OM	50	25	0	0	1	6	4	1	1
41	M	4	Unknown	No	3	53	0	-	-	-	0	12	na	12	na	0.47	na
42	F	9	Structural	Yes	2	17	0	-	-	-	0.05	0	na	4	na	0.93	na

Table 2 (Continued)

Sub-ject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
43	F	8	Structural	Yes	3	42	0	-	-	-	0.01	6	3	4	2	1	1
44	M	7	Unknown	Yes	2	55	0	-	-	-	0.05	7	3	2	2	0.86	0.86
45	M	4	Genetic	Yes	1	58	4	OM	75	5	0.05	10	na	10	na	1	na
46	M	12	Genetic	Yes	5	95	1	OM	100	3	0.05	11	na	18	na	0.61	na
47	M	10	Structural	No	1	60	0	-	-	-	0.01	6	na	8	na	1	na
48	F	6	Structural	Yes	1	47	0	-	-	-	0.24	na	na	na	na	na	na
49	M	12	Unknown	Yes	2	4	2	TC, T>30	100	33	0.01	11	na	14	na	0.93	na
50	F	7	Unknown	No	3	27	9	TC, OM	78	54	0.01	10	na	na	na	0.90	na
51	M	9	Genetic	Yes	4	38	10	TC, OM	100	22	0.06	9	na	12	na	0.91	na
52	F	10	Unknown	No	1	60	2	TC	100	6	0.03	7	na	7	na	0.89	na
53	M	5	Unknown	No	4	108	15	OM	67	37	0.02	11	11	15	na	0.83	0.45

ASM anti-seizure medication, *CSI* Caregiver stress index, *F* female, *FAR* false alarm rate, *HK* hyperkinetic, *M* male, *na* not available, *OM* other major, *PPV* positive predictive value, *PSQI* Pittsburgh sleep quality index, *TC* tonic-clonic, *T>30* tonic >30 seconds, *QoL* quality of life., *yrs* years.

[a] *Overall seizure sensitivity for all seizure types combined.*

[b] *All recorded data of this participant was excluded due to insufficient video data.*

indicated that ≥2 items (of 13) on the CSI were no longer difficult for them to handle. Caregiver sleep quality and QoL did not significantly change following NightWatch usage (mean total PSQI score=7.9 vs. 6.7, p=.117; mean total EQ-5D-5L score = .9 vs. .9).

Caregiver's expectations and experiences

Table 3 summarizes the results of the online questionnaires on caregivers' expectations and experiences with NightWatch. Trial participants had high expectations of the NightWatch before the start of the trial. Nearly all users reported that NightWatch was easy to use. Postintervention, caregivers were asked if they decided to keep using NightWatch (which meant they needed to buy it); 32% of caregivers (n=7) (strongly) agreed, 18% (n=4) were neutral, and

Table 3 Caregiver's expectations of and experiences with NightWatch

Evaluated item	Mean [SD] on the 5-point Likert scale
Expectations (n=25)	
I expect NightWatch to be a reliable device	3.83 [0.38]
I expect NightWatch to be useful	4.25 [0.53]
I expect NightWatch to provide a safe night	3.79 [0.42]
I expect NightWatch to be our last resort	3.17 [0.82]
I don't expect that much, I'll wait and see	2.92 [1.06]
I expect that NightWatch must prove itself	3.54 [0.78]
I need a seizure detection device (other than the ones I might have used before)	4.13 [0.85]
I expect to keep using the device after the trial	3.71 [0.69]
Experiences (n=22)	
I am overall satisfied with using NightWatch as a device	3.05 [1.09]
I am satisfied about the fixation of NightWatch on the upper arm	3.36 [0.95]
I am satisfied about the way NightWatch alerts during a seizure	2.77 [1.15]
NightWatch met my expectations	2.55 [0.96]
NightWatch is simple to use	4.41 [0.73]
For me, the NightWatch is a reliable device	3.18 [0.96]
I could better let go of the care of my child during the night, because I trusted the NightWatch	2.86 [1.04]
My child was not bothered by NightWatch	3.77 [1.02]
Other members of our family were not bothered by the device	3.32 [1.13]
I believe that I'm better able to report the number of seizures of my child to our neurologist	3.14 [1.28]
I will keep using the NightWatch after the trial	2.77 [1.23]

50% (n=11) disagreed. Reasons to differ included a decrease in seizure frequency during the trial (n=5); high FAR (n=3), too expensive to purchase (n=2), and skin irritation (n=1).

DISCUSSION

This phase 4 SDD trial provides class II evidence that NightWatch accurately detects nocturnal major motor seizures in children (median sensitivity=100%). Besides high sensitivity for the detection of convulsive seizures, NightWatch also showed good performance in detecting HK and OM motor seizures in children. NightWatch was well tolerated and easy to use. Caregivers reported a positive effect on their experienced stress during NightWatch use, whereas their quality of sleep and QoL did not change significantly.

Strengths and limitations

Strengths of the PROMISE trial include the prospective, home-based, video-controlled design, long-term follow-up, and many recorded nights and seizures. The long-term follow-up helped to estimate the performance reliably. Contextual conditions may significantly impact the seizure detection algorithm's performance. For instance, electrocardiography-based algorithms yielded poorer results in freely moving people than in those lying in bed.[19] The home environment allowed us to examine a realistic setting, but we could also evaluate user satisfaction. One of the challenges with a home-based approach is the risk of missing seizures due to the lack of continuous EEG supervision, which may inflate sensitivity. To reduce this bias, we applied different screening methods. First, we asked the caregivers to record all seizures. Second, trial nurses screened 5% of all video recordings. Third, we retrospectively ran an automated, previously validated video detection algorithm on all tracings.[16,17] During this process, we found that the frame rate of the video recordings was not constant, hampering performance of the method compared to previous work.[16,17] Nonetheless, the video algorithm accounted for 67% of all false negative detections. In the randomly selected 5% of all data that we visually reviewed, we found 25 seizures in total (NightWatch detections+detected false negatives). If this number is representative for the complete dataset, we would expect 25×20=500 seizures in total. However, we found 552 seizures with our approach, suggesting that our method probably detected most of the seizures. Another challenge of our home- and video-based approach concerns the observer reliability. We expect that the reliability depends on the seizure type,

with likely high accuracy for the identification of TCs and longer tonic seizures, whereas other seizure types (e.g., certain types of HK seizures and the seizures that we classified as "OM") can be more challenging to distinguish from normal or sleep-related behavior. Nevertheless, in our previous NightWatch trial in adults we found a substantial interobserver agreement for the different seizure types used in this study.[14] A significant advantage of our approach over conventional phase 4 studies includes the video-controlled design that allowed us to verify user feedback. Users may recognize nonepileptic events as seizures or label seizure-related alarms false if the caregiver arrives late and the seizure is shortlasting. Another strength includes the detection of a broad range of motor seizures. A limited number of caregivers completed the online questionnaires, which may have biased results. This bias could work both ways; people who are either satisfied or unsatisfied may doubt the usefulness of the questionnaires, which reflects a realistic scenario of adherence in practice. Children of caregivers who did not complete the full questionnaire had on average fewer recorded nights during the intervention period compared to children of caregivers who did. This difference was not statistically significant but may have caused bias. The questionnaires provide some indicators but fall short of understanding the experienced value of NightWatch given the many interfering contextual factors (e.g., fluctuating disease course and parental coping). We addressed this limitation by conducting qualitative, in-depth interviews with 23 parents of 19 children, including dropout cases. We found that the experienced value of NightWatch resulted from an interplay of contrasting factors: on the one hand, the amount of assurance it could offer to reduce their fear of losing their child and the associated protective behavior, and conversely, their resilience to handle the potential extra burden of care (e.g., false alarms).[8]

Related research

Unlike other commercially available SDDs, NightWatch demonstrated relatively high sensitivity and a slightly lower FAR.[1,11,20] A recent meta-analysis on the performance of wearable SDDs yielded a mean sensitivity of 91% for detecting convulsive seizures and an overall FAR of .08/h.[21] However, it is hard to compare our results with other devices, because almost none provides phase 4 studies or focuses on children or people with learning disabilities. Other devices usually include only small datasets with short-term follow-ups and recordings in a hospital or epilepsy monitoring unit. Another critical contrast with previous

SDD trials consists of the seizure types; most trials focused on convulsive seizures only, whereas we included a broader range of significant motor seizure types. Previous surveys indicated that incorporating a broader range of seizures other than TCs may better meet the users' needs.[22-24] Unlike our previous video-controlled trial in adults, NightWatch sensitivity in this pediatric cohort is slightly higher, but so is the FAR.[14] The FAR is partly explained by a high seizure burden, as almost one third of false alarms are related to seizures that did not meet our criteria for clinically urgent. The remainder is related to arousals or nonepileptic rhythmic movements. NightWatch algorithm corrects for individual baseline HR, but HR fluctuations and nonepileptic rhythmic movements may trigger false alarms. HR profiles of children differ from adults and are characterized by higher resting values and more significant variability.[25,26] Children, particularly those with developmental disorders, may also present with challenging behavior and sleep-related rhythmic movements.[27] Children with comorbid movement disorders were excluded from the trial, yet we did encounter some children with excessive or restless movements and body rocking. Accordingly, our post hoc analysis indicated that children with learning disabilities had higher FARs. We expect lower FAR in older cohorts and cohorts with less challenging behavior. Approximately one third of the participants did not experience a significant seizure during the intervention period. In parallel to this trial, children were treated by their neurologist and in 15 cases higher doses of antiseizure medications were given during the intervention compared to baseline, which might explain the lower seizure frequency. Possible other reasons for this include the reflection of a natural course of seizure frequency, or perhaps even a protective effect of SDD usage providing reassurance. Clinical trial simulations with time running forward and in reverse revealed that the placebo response is almost entirely attributable to the natural variability of epilepsy.[28] Prospective, real-time, video-controlled performance studies in a home environment are scarce. Only two other phase 4 SDD studies have been performed, including the previous NightWatch study assessing its performance in adults living in a residential care facility.[1,14,29] NightWatch scored high on user-friendliness, and caregivers indicated that implementation facilitated a timelier response and more freedom. In contrast, the burden of care remained unchanged.[14] This is in line with our results of lower stress scores following NightWatch usage. The second in-field study examined the applicability and usability of a wearable accelerometer device (Epi-Care) for detecting focal to bilateral convulsive seizures.[29] Most users were overall satisfied with the device,

many indicated that the use of the device had resulted in fewer seizure-related injuries, and only a small group stopped using the device due to reasons related to it (e.g., high FAR, irritation or discomfort, low effectiveness). The study included a large population and longterm follow-up, but device performance data were based only on seizure diaries. Nearly all people with epilepsy included in these phase 4 studies lived in residential care facilities, reflecting a different ambulatory setting and possibly different user needs than in our study.[14,29] A pilot study on 10 adolescents with epilepsy and their families showed an insignificant increase in QoL (Quality of Life in Epilepsy Inventory for Adolescents 48) while using a wearable SDD (SmartWatch) for 6 months.[30] A larger survey study found that most SDD users experienced reduced anxiety from device usage. At the same time, there was no significant difference in overall HR-QoL between SDD users and nonusers.[31] In a second large survey study, the majority of SDD users (including one third of users of NightWatch) agreed that using the device improved their QoL (median=6 on a 7-point Likert scale).[32] Another large study followed families of children with newly diagnosed epilepsy. Those who wanted to use an SDD (approximately half of the families) were randomly allocated to the Epi-Care or an audio baby monitor.[33] QoL improved significantly over time in all parents, suggesting that QoL increases independently of SDD usage. We recently performed an economic assessment of NightWatch. We found no significant changes in quality-adjusted life years after NightWatch intervention. Nonetheless, we demonstrated a decrease in societal costs (€775 reduction during the 2-month intervention period), suggesting that NightWatch might be a cost-effective addition to usual care for children with severe epilepsy living at home.[34] We found a small but significant reduction in caregiver stress, possibly partly explained by the short intervention period. The latter might also explain why we could not find a considerable change in caregivers' quality of sleep and life. Caregivers were optimistic about the practical use of NightWatch. Nonetheless, not all wanted to continue NightWatch, mainly due to cost (NightWatch is not yet reimbursable in the Netherlands), FAR, or seizure remission, thus emphasizing that SDD implementation is a multifactorial process. Acceptance of a device into a family home depends on device performance and even more on contextual factors like the burden of care8 and taking time to trust the device.[35,36] Future SDD studies should focus on ways to reduce FAR, which could facilitate implementation. Possible avenues include validating multiple algorithms that improve performance in specific subgroups (e.g., by focusing more on HR parameters

than movement) and applying machine learning techniques to create individual-specific algorithms.[37,38] These approaches also have the potential of addressing the varying needs among users regarding the trade-off between true positives and FAR.[21]

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