FULL-LENGTH ORIGINAL RESEARCH

Detection of generalized tonic–clonic seizures using surface electromyographic monitoring

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Summary

Objective: **A prospective multicenter phase III trial was undertaken to evaluate the performance and tolerability in the epilepsy monitoring unit (EMU) of an investigational wearable surface electromyographic (sEMG) monitoring system for the detection of generalized tonic–clonic seizures (GTCSs).**

Methods: **One hundred ninety-nine patients with a history of GTCSs who were admitted to the EMU in 11 level IV epilepsy centers for clinically indicated video-electroencephalographic monitoring also received sEMG monitoring with a wearable device that was worn on the arm over the biceps muscle. All recorded sEMG data were processed at a central site using a previously developed detection algorithm. Detected GTCSs were compared to events verified by a majority of three expert reviewers.**

Results: **For all subjects, the detection algorithm detected 35 of 46 (76%, 95% confidence interval [CI] = 0.61–0.87) of the GTCSs, with a positive predictive value (PPV) of 0.03 and a mean false alarm rate (FAR) of 2.52 per 24 h. For data recorded while the device was placed over the midline of the biceps muscle, the system detected 29 of 29 GTCSs (100%, 95% CI = 0.88–1.00), with a detection delay averaging 7.70 s, a PPV of 6.2%, and a mean FAR of 1.44 per 24 h. Mild to moderate adverse events were reported in 28% (55 of 199) of subjects and led to study withdrawal in 9% (17 of 199). These adverse events consisted mostly of skin irritation caused by the electrode patch that resolved without treatment. No serious adverse events were reported.**

Significance: **Detection of GTCSs using an sEMG monitoring device on the biceps is feasible. Proper positioning of this device is important for accuracy, and for some patients, minimizing the number of false positives may be challenging.**

KEY WORDS: **Clinical trials, Epilepsy monitoring, Generalized seizures, Convulsions, Grand mal seizures, Wearables.**

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Statistical Analysis was performed by Luke Whitmire, PhD of Brain Sentinel, Edward Jones, PhD of Texas A&M University, and August Blackburn, PhD, independent consultant.

Key Points

- Epilepsy patients with frequent GTCSs are at increased risk for injuries and SUDEP
- sEMG signal recorded on the arm during GTCS is distinct from that recorded during other types of arm movements
- This is a prospective phase III trial to evaluate the performance and tolerability of a wearable sEMG monitoring system for detection of GTCSs in the EMU
- For subjects who wore the device properly placed over the belly of the biceps muscle, the system detected 100% of GTCSs, with a mean FAR of 1.4 per 24 h
- FAR for adult subjects properly wearing the device varied between 0 and 10 per 24 h, indicating that some patients who use the device may experience excessive false alarms

The prevalence of active epilepsy (patients with at least one seizure in the past 5 years), is 0.4–1.0% worldwide.[1] In a study of one city in France, Picot et al.[1] found that 37.5% of patients with active epilepsy had suffered at least one generalized tonic–clonic seizure (GTCS). The prevalence of epilepsy patients with frequent GTCSs is unknown, but is probably 10–20% of patients with active epilepsy, and these are the patients who are most at risk for injuries,[2,3] sudden unexpected death in epilepsy (SUDEP),[4] and mortality from any cause.[5] Status epilepticus (SE), a life-threatening medical emergency that requires prompt intervention, often begins as a GTCS.[6] Early identification of the GTCS and intervention promises to decrease morbidity and mortality in cases of SE[7] and SUDEP.[8] There is a need for a cost-effective, easy-to-use, and accurate device that patients can wear continuously to detect GTCSs in both inpatient and outpatient settings.

The surface electromyographic (sEMG) signal recorded on the arm during the tonic and clonic phases of GTCSs is distinct, both in amplitude and morphology, from that generated by typical movements and other seizure types, permitting detection through sEMG monitoring.[9] A previous single site study of an sEMG detection algorithm in the epilepsy monitoring unit (EMU) detected 95% of 20 GTCSs recorded in 11 epilepsy patients with only one false-positive detection.[10] We present results of a multicenter study designed to examine the performance and tolerability of the Brain Sentinel Monitoring and Alerting System worn on the arm in the EMU.

Methods

Standard protocol approvals, registrations, and patient consents

This trial (Brain Sentinel Protocol 4.1; ClinicalTrials.gov identifier: NCT01874600; principal investigator: J.E.C.) was conducted at 11 level IV National Association of Epilepsy Center[11] sites in the United States. The U.S. Food and Drug Administration (FDA) granted an exemption from Investigational Device Exemption submission requirements due to nonsignificant risk. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, the Clinical Trial Directive 2001/20/EC, and U.S. Code of Federal Regulations Part 21. Trial protocol, amendments, and informed consent were reviewed by national regulatory authorities and independent ethics committees or institutional review boards for each site. Before participation, all patients or legally authorized representatives gave written informed consent. Standards for Reporting Diagnostic Accuracy Studies (STARD) are used for reporting results.[12]

Subjects

Prospective subjects were aged 3–72 years with a history of GTCSs (either primary GTCSs or partial onset seizures with secondary generalization) admitted for EMU monitoring as part of their standard clinical care. Subjects were required to have an upper arm circumference adequate for proper fit of the device (≥14 cm).

sEMG recording

A custom-designed device for recording sEMG data was used (Fig. S1) that includes a commercial foam-backed electrode patch containing three pregelled, Ag/AgCl surface electrodes (1-cm diameter and 1 cm apart in a triangular configuration; Multi Bio Sensors, El Paso, TX, U.S.A.). Recording electrodes were placed transversely over the belly of the biceps brachii muscle with the reference electrode oriented proximally. The electrode patch adhered to the skin with an acrylic-based adhesive, and the weight of the device was supported by an arm band. The electrical components of the applied device consist of an instrumentation amplifier, filtering network, and microcontroller designed to amplify and continuously record 1-kHz sampled sEMG, analyze sEMG for potential seizure activity, and transmit potential seizure alerts via Wi-Fi to a base station (BSN) computer. See Figure S1 for an example of the sEMG signal recorded from a GTCS.

The BSN is a laptop personal computer that communicates with both the monitoring device and a remote Brain Sentinel secure server. The BSN is designed to alert caregivers and patients to loose electrodes, Wi-Fi connection issues, and potential GTCSs using visual and auditory alarms. For this study, auditory and visual alerts generated by the device were muted to maintain blinding and study site personnel (excluding physicians) received only alerts related to operational issues (e.g., loose electrodes, connection issues, and low batteries). Subjects, direct care providers, and independent video-electroencephalographic (vEEG) reviewers were blinded to potential GTCS alarms.

All sEMG data recorded by the device were processed at a central site using the detection algorithm developed during the previous single site trial,[10] at a range of threshold settings (95–255, sampled at increments of 10). Threshold settings were measured in arbitrary units and were empirically derived from previous sEMG recordings from the biceps during periods of rest and during maximum voluntary contractions.

Trial design

This is a prospective STARD-compliant[12] (see Appendix S4) multicenter phase III trial of an investigational sEMG monitoring system for the detection of GTCSs that assessed performance and tolerability in the EMU. The device was attached to the subject's biceps on either side for continuous monitoring (Fig. S2) and was taken off of the arm and replaced every 12 h during battery changes by the study coordinator or clinical staff. Once per day, subjects were questioned about adverse events (AEs) and the skin where the device was placed was examined. Images of device placement were captured from the vEEG records and were reviewed by three independent reviewers (User-View, Raleigh, NC, U.S.A.) every time the device was placed or replaced onto the subject's arm. Devices that were placed >45° from the midline of the anterior portion of the biceps were considered to be improperly placed. Demographic information, recent changes to the subject's antiepileptic drugs during the admission, seizure history, and body measurements (e.g., height, weight, and mean upper arm circumference) were recorded to monitor for selection bias.

System detections and GTCSs identified by clinical care providers were independently adjudicated by vEEG reviewers blinded to system detections and sEMG recordings from the biceps. vEEG reviewers were a panel of epileptologists with subspecialty certification in Epilepsy from the American Board of Psychiatry and Neurology, who were not study site investigators (G.M.J., O.V.L., L.C.M.).

Statistical analysis

Statistical analysis was performed in R version 3.2.5[13] and MATLAB version 9.0.0.341360 (MathWorks, Natick, MA, U.S.A.). All study subjects were included in the intent to monitor cohort (IMC). Subjects were included in the properly placed cohort (PPC) if two of the three or more placement reviewers classified the device placement as proper and if there were no technical problems that prevented sEMG data acquisition or storage (as described below). Subjects excluded from the PPC were placed in the improperly placed cohort (IPC). Cohort demographics were analyzed using a generalized linear model (GLM) with a logit link function. Cohort (IPC vs PPC) was treated as the dependent variable, and the demographics (height, weight, gender, etc.) were treated as predictor variables.

The time of bilateral appendicular tonic motor manifestation of the GTCSs was compared to system detections to measure performance. Independent of primary or secondary generalization, seizures were counted as GTCSs if there was video evidence of a bilateral tonic phase followed by a bilateral clonic phase. Focal seizures with either tonic or clonic movements and/or movements that were unilateral and that did not evolve into GTCSs were not counted as GTCSs. A majority rules approach was taken by the vEEG reviewers to identify GTCSs, which were required to involve a tonic phase followed immediately by a clonic phase.[14] Gwet's AC2[15] was used to calculate inter-rater agreement for device placement and categorization of events as GTCSs.

Definitions for performance metrics are given in Appendix S1. Under the guidance of the FDA, the primary endpoint of the study was chosen to be confirmation that the device has a positive percentage agreement (PPA) of at least 70%, with the lower 95% confidence limit (LCL) calculated from the binomial exact method across a range of detection threshold settings. The study was not designed to identify an ideal threshold setting.

Results

Patient allocation and demographics

Between August 2013 and December 2015, a total of 199 subjects were recruited into the IMC. Fifty subjects (the IPC cohort) were excluded from the PPC for the following reasons: sEMG data accidentally not archived for reprocessing (14 subjects), faulty initial device setup (three subjects), device consistently misplaced on the arm (29 subjects), and subject consented but device was never placed (four subjects). Twenty-nine of the study subjects withdrew from the study early, but had sEMG data recorded prior to exiting that were included in the IMC and PPC analyses. Reasons for early withdrawal are summarized in Table S1. Continuous and nominal characteristics of subjects in the PPC and IPC are listed in Table 1. The overall effect of race was tested using a Wald test and was suggestive but not statistically significant ($p = 0.059$). A likelihood ratio test indicated that the GLM is a better fit than an empty model ($p = 0.045$). Overall, no statistical differences were found in demographic characteristics between the PPC and IPC cohorts or across sites.

While being recorded with sEMG, a total of 37 (19%) subjects in the IMC and 24 (16%) subjects in the PPC experienced at least one GTCS. A total of 46 GTCSs were recorded in the IMC and 29 GTCSs were recorded in the PPC. Five subjects in the PPC and eight subjects in the IMC had two or more GTCSs. Only one subject had three or more GTCS: an individual in the IPC who experienced five GTCSs. Only the first two events were included in the analysis to reduce subject bias. Fifty-nine subjects in the IMC were children or adolescents (see Table 2). IMC and PPC subjects were monitored for a total of 9,237 h (mean = 54.7 h per subject) and 7,369 h (mean = 51.2 h per subject), respectively. The IRA was high for confirmation of correct

Table 1. Comparison of real value and nominal characteristics of PPC subjects and IPC subjects (IMC subjects excluded from the PPC)

	IPC subjects		PPC subjects					
	n[a]	Mean	n[a]	Mean	Odds ratio[b]	Lower 95% CI	Upper 95% CI	p
Medications, n	49	2.9	149	2.3	0.70	0.52	0.932	0.016
Seizures/mo	49	21.9	146	17.2	1.00	0.99	1.01	0.85
Years with seizures	49	12.0	148	13.6	1.02	0.99	1.06	0.23
Height, in.	50	65.4	148	65.6	0.89	0.74	1.03	0.17
Weight, lbs	50	174.8	148	178.7	1.02	0.99	1.07	0.21
BMI	50	28.4	147	28.2	0.85	0.66	1.05	0.17
Age, yr	50	30.7	149	31.9	1.00	0.96	1.03	0.91
MUAC, cm	49	26.1	147	28.6	1.05	0.99	1.12	0.11
	n	%	n	%	Odds ratio[c]	Lower 95% CI	Upper 95% CI	p
Adult, yes	33/50	66	107/149	72	1.14	0.37	3.45	0.81
Gender, male	21/50	42	69/149	46	1.12	0.44	2.87	0.81
Self-reported ethnicity								
Hispanic, yes	6/50	12	5/149	3	1.05	0.10	9.38	0.96
Self-reported race								
Race, white	28/50	56	107/149	72	10.11	1.60	9.81	0.021
Race, black	16/50	32	40/149	27	6.83	1.03	6.87	0.061
Race, other[d]	6/50	12	2/149	1				

BMI, body mass index; CI, confidence interval; IMC, intent to monitor cohort; IPC, improperly placed cohort; MUAC, mean upper arm circumference; PPC, properly placed cohort.

[a]Data were not recorded for some fields in some subjects.

[b]Odds ratio and probability values were estimated using a generalize linear model with a logit link function.

[c]Odds ratios presented for race are relative to those grouped together as "other."

[d]Individuals not identifying as white or black were grouped together as "other."

position of device placement (AC2 = 0.74) and for vEEG identification of GTCSs (AC2 = 0.78).

Performance analysis

For the IMC, the detection algorithm detected 35 of 46 (76%, 95% confidence interval [CI] = 0.65–1.0) GTCSs with a mean false alarm rate (FAR) of 2.5 per 24 h at a threshold setting of 145. For the PPC, the system detected 100% of the GTCSs with a mean FAR of 1.4 per 24 h at a threshold setting of 145. Performance measures for the IMC and PPC are summarized in Figure 1 and Table 3. Because the pilot study[10] found that both the biceps and the triceps contracted in phase during GTCSs, it was initially thought that location of placement on the arm did not matter for performance. But because the device recorded from two electrodes placed transversely on the arm, placement of the device between the biceps and triceps caused in-phase cancellation, severely attenuating the sEMG signal. (For further details, see Appendix S2 and Fig. S3.) After this was discovered, between June and November 2014, staff at all study sites were retrained to place the device over the midline biceps. For the PPC, the lowest threshold setting that detected 100% of GTCSs was 145 and the highest threshold setting that retained the ability to detect >70% (LCL) of GTCSs was 215 (at this threshold setting, the FAR was reduced to 0.93 per 24 h).

There were 968 false alarms (FAs) in the IMC and 442 FAs in the PPC (Table 3). FAs occurred in 112 of 178 (63%) IMC subjects and 85 of 149 (57%) PPC subjects and were not evenly distributed across study subjects. Sixty of the subjects generated only 1–5 FAs each, whereas five of the subjects generated 17–40 FAs (30% of all FAs observed). Sixty-four percent of FAs occurred during activity, and 62% of FAs contained signal artifact commonly associated with loose electrodes. For all subjects that experienced a GTCS, and at the threshold setting of 145, the number of positive GTCS detections per FA varied considerably among subjects (Fig. 2). For all subjects, the positive predictive value (PPV) was 3.5% and 6.2% in the IMC and PPC, respectively. Observable causes for FAs (generated in real time at a threshold of 175) based on the vEEG recording are listed in Appendix S3. The summary of the time to alert for the device is found in Table 3. The average delay between vEEG reviewer-marked events and system detections in the IMC and PPC at a threshold setting of 145 is 7.45 s (range = 30.8–25) and 7.75 s (range = 30.8–25), respectively. A plot of time to alarm versus consensus vEEG reviewer opinion of the time of occurrence of all GTCSs is depicted in Figure S4. For the six subjects who had two GTCSs detected, the mean difference in time to alarm between the two detections was +5.53 (range = −10.5 to 21.5), with one subject switching detection time from before to after onset based on vEEG review.

Table 2. Summary of age and placement cohorts

	PPC	IPC	IMC
Adults (>21 years)	106	34	140
Adolescents (12–20 years)	35	13	48
Children (<12 years)	8	3	11
Total	149	50	199

IMC, intent to monitor cohort; IPC, improperly placed cohort; PPC, properly placed cohort.

AEs

Twenty-nine subjects withdrew from the study during sEMG monitoring (15%). Reasons for voluntary withdrawal included AEs (n = 17, 9%), usability/operationality (n = 6, 3%), withdrawal without reason (n = 4, 2%), and injury not related to the study (n = 2, 1%). A total of 28% (55 of 199) of subjects connected to the device reported an AE during the study. All AEs were reported to be mild to moderate, and no serious AEs were reported. AEs were evenly distributed across days of use (average = 3.5, range = 1–8 days). Mild skin irritation (similar to typical reaction to an adhesive bandage) was the most commonly reported AE, occurring in 17% (34 of 199) of the study population. Moderate skin irritation was the second most frequent event, occurring in 5% (11 of 199). The outcomes of subjects reporting skin irritation, at telephone follow-up 30 days after EMU discharge, are listed in Table 4. Other AEs due to device electrodes included skin tears (n = 5, 2.5%), general discomfort (n = 2, 1%), blister (n = 1, 0.5%), and bruising (n = 1, 0.5%). A device usability questionnaire was given to subjects. Of 168 respondents, 23% (38 of 168) reported that the device was uncomfortable to sleep with. Forty-two percent (16 of 38) of these subjects reported that they would ask their physician to prescribe the system, 26% (10 of 38) reported that they would not, 13% (five of 38) had no opinion, and 18% (seven of 38) did not comment.

Discussion

This study shows that an EMG-based seizure detection system can perform reasonably well in detecting GTCS. There is a real need for a cost effective, easy-to-use, and accurate wearable detector for GTCS in the hospital or home environment, and methods such as this hold promise. Although it was not foreseen when the study was being planned, placement of the device over the belly of the biceps was found to be important for optimal functioning of the device, greatly enhancing sensitivity. False positive detections did occur and enhancement in specificity is desirable in the future. We believe such a seizure detection system may prove useful to families and caregivers, by providing the ability for real-time detection and intervention during or immediately after a GTCS.

The system provided timely detection of GTCS, within an average of 7.7 seconds of the onset of bilateral appendicular tonic motor manifestations as annotated by expert vEEG raters. This rapid detection is valuable given that timely treatment of seizure events can be life-saving. The consistency of the detection latency within subjects could not be thoroughly assessed because only five patients experienced two GTCS during monitoring. (Most subjects only experienced one GTCS.) All five of these GTCS were detected and there was no similarity or correlation in detection latency within subjects. In some cases, where the monitoring device alarmed before initial tonic motor

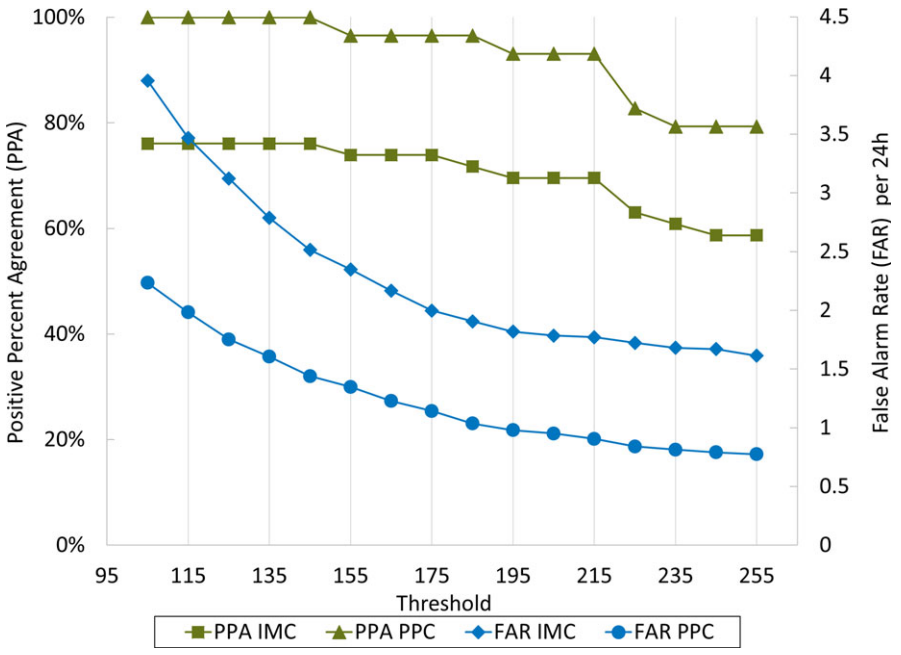

Figure 1.
Positive percent agreement (PPA) and false alarm rate (FAR) per 24 h across a range of threshold settings for the intent to monitor cohort (IMC) and properly placed cohort (PPC).
Epilepsia © ILAE

Table 3. GTCS detection results at threshold setting of 145

Cohort	IMC, all, n = 199	IMC, adults, n = 139	PPC, all, n = 149	PPC, adults, n = 106
Total GTCSs per epileptologists	46	33	29	21
GTCSs detected by device	35	27	29	21
PPA (95% CI)[a]	76% (61–87%)	82% (65–93%)	100% (88–100%)	100% (84–100%)
Total false positives	968	646	442	357
Total hours of sEMG	9,237	7,142	7,369	5,637
PPV for all subjects	3.5%	4%	6.2%	5.6%
PPV for subjects experiencing a GTCS	11%	9.7%	20%	18.6%
Mean false alarm rate per 24 h (range)	2.52 (0–349)	2.16 (0–47)	1.44 (0–16)	1.52 (0–10)
Time to alarm[b]				
Mean, s	7.45	5.53	7.75	5.40
Median, s	7.38	6.67	9.26	6.67
Standard error of the mean, s	2.01	2.35	2.31	2.85
Range,[c] s	−30.82 to 25.06	−30.82 to 25.06	−30.82 to 25.06	−30.82 to 25.06
Time to alarm for delayed alarms[d]				
Mean, s	11.83	11.00	12.03	11.09
Median, s	12.79	11.00	13.90	12.79
Standard error of the mean, s	1.40	1.57	1.52	1.75
Range, s	0.78–25.06	1.3–25.06	0.78–25.06	1.3–25.06

CI, confidence interval; GTCS, generalized tonic–clonic seizure; IMC, intent to monitor cohort; PPA, positive percentage agreement; PPC, properly placed cohort; PPV, positive predictive value; sEMG, surface electromyography; vEEG, video-electroencephalography.

[a]As compared to independent review.

[b]Value includes false alarms generated in subjects who did not experience a GTCS.

[c]The negative numbers included in the range reflect monitoring alerts that precede the time marked by the vEEG reviewers.

[d]Delayed alarms are alarms that occurred after the consensus time of GTCS onset based on expert vEEG review.

manifestation, the alarm was triggered by motor manifestations that precede the tonic phase of the GTC.

Mild to moderate skin irritation occurred in 23% of subjects in this study. It is unknown if long-term use of the system may increase this occurrence and lead to decreased compliance over time. The first generation of this device, which was tested in this study, was rather heavy (8 oz.), but was well- tolerated by subjects, with only 9% of subjects withdrawing from the study due to mild or moderate AEs, which were mostly mild skin irritation and all resolved without sequelae. Because it was more difficult to recruit pediatric subjects (less than age 13), the number of GTCS recorded in pediatric subjects (n = 2) is limited. Since it is not known if the device will perform just as well in children and adolescents, the pivotal trial continues to be open to recruit more pediatric subjects to verify this.

Two devices with an alternative approach to detection of GTCS by measurement of wrist accelerometry are being investigated for the detection of GTCS. A study of the EpiCare system developed by Danish Care Technology ApS demonstrated a sensitivity of 89% for detection 39 GTCS in 20 patients in the EMU with a FAR of 0.2 per 24 h.[16] A recent study of the SmartWatch system being developed by SmartMonitor, reported that the device detected 12 of 13 GTCS (92.3%) in nine patients in the EMU with 81 FAs (with the FAR not detailed).[17] A previous study of the SmartWatch had shown only a 31% sensitivity for detecting GTCS (with the FAR not reported).[18] No AEs have been reported with use of wrist accelerometry devices.[16–18] In addition, the low power consumption of accelerometry monitoring and Bluetooth transmission of captured data allows for battery life of up to 5 days.[18] These devices, which show promising results from pilot studies, are not yet FDA approved.

When FDA review is needed prior to marketing a device, the FDA will either (1) "clear" the device after reviewing a premarket notification, otherwise known as a "510(k)" application (named for a section in the Food, Drug, and Cosmetic Act) if there is a predicate device or (2) "approve" the device after reviewing a premarket approval (PMA) application (if there is no predicate device). As there was no predicate device in this case, the Brain Sentinel system was automatically categorized as a class III device, which would usually require a PMA application. But since the FDA determined the device to be a nonsignificant risk device, "clearance" (rather than "approval") was granted through the "de novo" application pathway, and not through a 510(K) application or a PMA application.

There are three significant weaknesses in this study. First, technical challenges arose early in the study and caused data loss from 46 subjects because of accidental data loss and suboptimal placement location of the device on the arm. Comparison of subjects who were excluded due to these technical challenges (the IPC) and subjects included (the PPC) showed no difference in subject characteristics. Improved placement training led to a decrease in the frequency of improper placement, and careful training was essential for optimal device use. Modifying the device placement training improved the accuracy of placement from 73% (76/104) to 93% (69/74) (verified by video

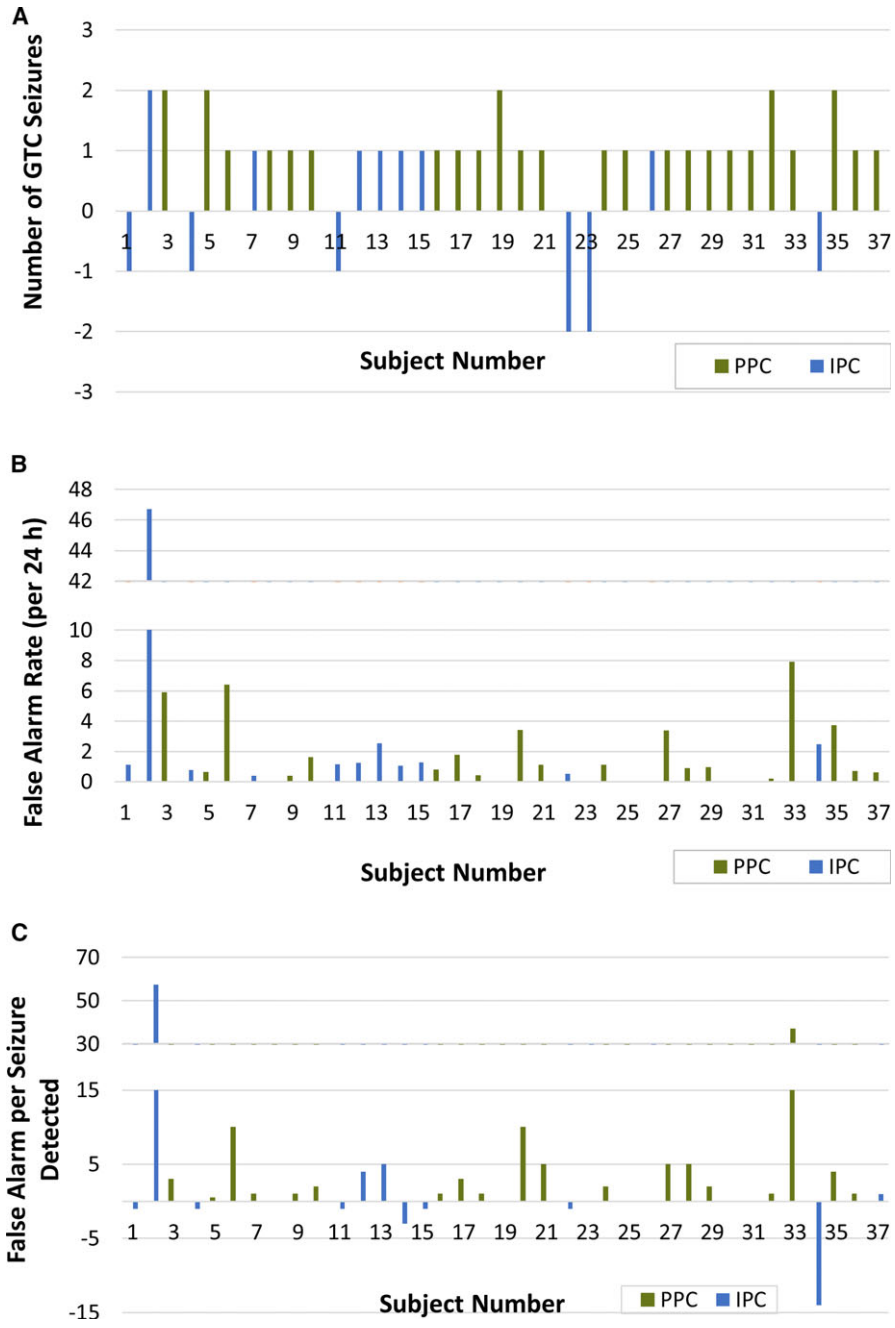

Figure 2.
Number of generalized tonic–clonic seizures (GTCSs) recorded, false alarm rate, and false alarms per GTCS detected for all subjects who had at least one GTCS during monitoring. Membership in the properly placed cohort (PPC) and improperly placed cohort (IPC) is indicated by color. (**A**) Positive values for true-positive GTCS detections and negative values for GTCSs that were not detected (false negatives). (**B**) The false alarm rate for all subjects. (**C**) A positive value for false alarms per GTCS detected in subjects in whom the device detected the GTCS and the number of false alarms as a negative value for subjects in whom the device failed to detect the GTCS.

review). Improved procedures for archiving of data were also implemented.

Second, the FAR was calculated for all subjects without regard to optimization for individual users. Using this method, the FAR generated by the device in some subjects was quite high. The FAR in all subjects (the IMC) varied from 0 to 349, with a mean FAR of 2.52 per 24 h. When the device was worn over the belly of the biceps (the PPC), the FAR was better, with a range of 0 to 16 and a mean of 1.44 per 24 h, but still too high in some subjects. The detection specificity needs to be higher to meet patient and physician expectations. Surveys of patients with epilepsy (and their caregivers) have shown that they would strongly consider applying and permanently using a device to detect seizures, especially if the device is wearable (removable) and worn either on the wrist or as a patch over an invisible body site.[19] As reported by Van de Vel et al.,[20] epilepsy patients, caretakers, and physicians prefer a seizure registration device with at least 90% sensitivity and a FAR such that there is, on average, no more than one FA per seizure detected (and one FA per week for those seizure- free). Since performance of the device reported here reaches this performance threshold in regard to sensitivity but not for FAR,

Table 4. Outcomes of subjects reporting skin irritation in the intent to monitor cohort

Outcome at 30 days after EMU discharge	Number of subjects with mild skin irritation	Number of subjects with moderate skin irritation
Resolved, no sequelae	23 (12%)	5 (2.5%)
AE still present, no treatment	2 (1.0%)	3 (1.5%)
AE still present, being treated	0	2 (1.0%)
Residual effects present, not treated	7 (3.5%)	0
Residual effects present, treated	1 (0.5%)	1 (0.5%)
Lost to follow-up	1 (0.5%)	0
Total	34 (17.1%)	11 (5.5%)

AE, adverse event; EMU, epilepsy monitoring unit.

improvements in the device are needed to decrease the number of false-positive detections. This was a first attempt to create a wearable sEMG system to detect GTCS and hopefully the next generation of the device, with better electrodes and with algorithm improvements, will provide better detection specificity. Physicians using the current system will be able to adjust the threshold setting to optimize performance and choose whether or not to continue using the device depending on whether patients and/or caregivers perceive it to be effective.

Third, this study shows that the system works in the EMU environment; however, how well it will work in the home environment remains to be seen. It is not known how well the device will be tolerated if worn in the home for extended periods of time, since this study just assessed tolerability during a few days of inpatient monitoring. In the home, there are additional challenges related to increased patient movement, placement of the study device, FAR, and tolerability. The device will have to be placed on the arm by the patient or caregivers, not a study coordinator, and the BSN and a continuous internet connection will need to be kept operational. A usability study has demonstrated that people with epilepsy can set up and operate the system safely and effectively.[21] The frequency of GTCS in the home environment may be less than that in the EMU, increasing the ratio of FAs per seizure detected. But physicians may be able to discern GTCS from non-GTCS sEMG patterns by review of previously recorded sEMG events and manipulate the threshold settings of the Brain Sentinel device to improve performance.

Wearable technologies promise to provide improved detection of clinically relevant events and continuous physiologic monitoring information to patients, caregivers, and health care workers. Since GTCS can cause patient injury and are associated with SUDEP, the device should be useful to provide a method for caretakers to check on patient safety shortly after a GTCS. The Brain Sentinel system is the first FDA-approved wearable device designed to be used in patients with epilepsy. It is designed to detect GTCS, provide visual and auditory alerts (at the system), and provide remote alerts sent by text, voice, and/or email message alarms to caregivers. It is also designed to provide an objective measurement of the frequency of GTCS in the outpatient setting and provide immediate warning of GTCS occurrence to medical staff working in EMUs. A Web-based portal has been developed which will allow physicians to log in to view detection times, adjust detection threshold settings, view sEMG signal, and listen to audio recorded during detection events.

Future research goals include improving device tolerability and studying the sEMG signal from the scalp recorded as part of standard EEG to determine whether it contains similar signals that could be used to detect GTCS in the EEG signal from EMU or ambulatory EEG monitoring. The Brain Sentinel system may also be useful as a diagnostic device if it can discriminate between GTCS and convulsive non-epileptic events. Additionally, advanced postprocessing analytics may provide chronic and single event seizure semiology information, thereby expanding the quality of available patient data.

Study Funding

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Conflict of Interest

Jonathan J. Halford has acted as a consultant for Brain Sentinel, Acorda, Eisai Medical Research, UCB Pharma, Lundbeck, Validus Pharmaceuticals, SK Life Sciences, and Upsher-Smith; receives funding from the National Institutes of Health (NIH; SBIR-IIB- 2R44NS064647-05A1); and has been an investigator for clinical trials funded by Acorda, Eisai, LCGH, GW Pharma, Lundbeck, Optima Neurosciences, UCB, and the Epilepsy Study Consortium. Michael R. Sperling has acted as a consultant for Medtronic (for protocol design, contract with Thomas Jefferson University; payment to Thomas Jefferson University) and Medscape (for continuing medical education activity); receives research funding from UCB Pharma, Sunovion, SK Life Sciences, Eisai, Pfizer, Glaxo, Accorda, Upsher-Smith, Neurelis, Marinus, Lundbeck, Brain Sentinel, and Medtronic; and has research contracts with Thomas Jefferson University, UCB Pharma, Sunovion, SK Life Sciences, Eisai, Pfizer, Glaxo, Acorda, Upsher-Smith, Neurelis, Marinus, Lundbeck, Brain Sentinel, and Medtronic. Dileep R. Nair receives funding from the NIH (RNS089212A_A7886P1), Brain Sentinel, and Neuropace. Dennis J. Dlugos receives funding from the NIH (1R01NS053998, 2U01NS045911, U01NS077276) and the Epilepsy Study Consortium. William O. Tatum receives a stipend from Elsevier as Editor-in-Chief of *Epilepsy & Behavior Case Reports*, royalties from Demos Medical Publishing and Springer Publishing, and grant support from Mayo Clinic; and has acted as a consultant for SK Life Science (safety board). Jay Harvey has acted as a consultant for UCB and Sunovion; and receives funding (as an investigator) for clinical trials by Acorda, SK Life, GW Pharma, UCB, Sage, and Marinus. Jacqueline A. French receives New York University (NYU) salary support for consulting work on behalf of the Epilepsy Study Consortium from Acorda, Adamas, Alexza, Anavex, Axcella Health, Biogen, BioPharm Solutions, Cerecor, Concert Pharmaceuticals, Eisai, Georgia Regents University, GlaxoSmithKline, GW Pharma, Marinus, Monteris, Nestlé Health Science, Neurelis, Novartis, Pfizer, Pfizer-Neusentis, Roivant, Sage, SciFluor, SK Life Sciences, Sunovion, Takeda, UCB,

Upsher-Smith, Xenon Pharmaceuticals, Zogenix, and Zynerba; has received personal compensation for serving as an Associate Editor of *Epilepsia*; and has received research grants from Acorda, Alexza, Eisai Medical Research, LCGH, Lundbeck, Pfizer, SK Life Sciences, Sunovion, UCB, Upsher-Smith, and Vertex, as well as grants from the Epilepsy Research Foundation, Epilepsy Study Consortium, Epilepsy Therapy Project, and National Institute of Neurological Disorders and Stroke; is on the editorial board of *Lancet Neurology*, *Neurology Today*, and *Epileptic Disorders*; is scientific officer for the Epilepsy Foundation, for which NYU receives salary support; and has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Eisai, GW Pharma, Marinus, Nestlé Life Sciences, Pfizer, Sage, SK Life Sciences, Takeda, UCB, Upsher-Smith, Zogenix, and Zynerba. John R. Pollard is part owner of Cognizance Biomarkers; and receives research support from GlaxoSmithKline, Cognizance Biomarkers, and SK Pharmaceuticals. Edward Faught has received consulting fees from Aprecia, Biogen, Eisai, Medscape, and UCB Pharma; has served on research data monitoring boards for Eisai, Lundbeck, Sage, and SK Life Science; and has received research funding from Brain Sentinel and UCB Pharma. Katherine H. Noe receives research funding from Neuropace. Thomas R. Henry receives research funding from the NIH (1U01NS088034-01, NS-058634-01A2), the National Science Foundation (CRCNS 15-595, award 1607835), the Centers for Disease Control and Prevention (subproject 00047299 of 1U48-DP005022-01), and Brain Sentinel. Gina M. Jetter and Octavian V. Lie have acted as consultants for Brain Sentinel. Lola C. Morgan receives funding from UCB, Upsher-Smith, and Sage Pharmaceuticals. Michael R. Girouard owns stock in and is employed by Brain Sentinel. Damon P. Cardenas and Luke E.Whitmire are employees of Brain Sentinel. Jose E. Cavazos owns stock in and is a consultant to Brain Sentinel. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Example of surface electromyographic signal recorded during a generalized tonic–clonic seizure.

Figure S2. Detection device and arm-worn components of the prototype Brain Sentinel generalized tonic–clonic seizure detection and warning system.

Figure S3. Example of surface electromyogram recorded with the Brain Sentinel generalized tonic–clonic seizure detection and warning system.

Figure S4. Plot of alarm latency for detection of generalized tonic–clonic seizures.

Table S1. Reasons for early withdrawal from the study.

Appendix S1. Definitions of performance metrics for automated detection.

Appendix S2. Analysis of false alarms.

Appendix S3. Location of surface electromyographic recording.

Appendix S4. Standards for Reporting Diagnostic Accuracy Studies checklist for the reporting of studies of diagnostic accuracy.