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Perspective

Non-electroencephalogram-based seizure detection devices: State of the art and future perspectives

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ABSTRACT

Introduction and purpose: The continuously expanding research and development of wearable devices for automated seizure detection in epilepsy uses mostly non-invasive technology. Real-time alarms, triggered by seizure detection devices, are needed for safety and prevention to decrease seizure-related morbidity and mortality, as well as objective quantification of seizure frequency and severity. Our review strives to provide a state-of-the-art on automated seizure detection using non-invasive wearable devices in an ambulatory (home) environment and to highlight the prospects for future research.

Methods: A joint working group of the International League Against Epilepsy (ILAE) and the International Federation of Clinical Neurophysiology (IFCN) recently published a clinical practice guideline on automated seizure detection using wearable devices. We updated the systematic literature search for the period since the last search by the joint working group. We selected studies qualifying minimally as phase-2 clinical validation trials, in accordance with standards for testing and validation of seizure detection devices.

Results: High-level evidence (phases 3 and 4) is available only for the detection of tonic-clonic seizures and major motor seizures when using wearable devices based on accelerometry, surface electromyography (EMG), or a multimodal device combining accelerometry and heart rate. The reported sensitivity of these devices is 79.4–96%, with a false alarm rate of 0.20–1.92 per 24 hours (0–0.03 per night). A single phase-3 study validated the detection of absence seizures using a single-channel wearable EEG device. Two phase-4 studies showed overall user satisfaction with wearable seizure detection devices, which helped decrease injuries related to tonic-clonic seizures. Overall satisfaction, perceived sensitivity, and improvement in quality-of-life were significantly higher for validated devices.

Conclusions: Among the vast number of studies published on seizure detection devices, most are strongly affected by potential bias, providing a too-optimistic perspective. By applying the standards for clinical validation studies, potential bias can be reduced, and the quality of a continuously growing number of studies in this field can be assessed and compared. The ILAE-IFCN clinical practice guideline on automated seizure detection using wearable devices recommends using clinically validated wearable devices for automated detection of tonic-clonic seizures when significant safety concerns exist. The studies published after the guideline was issued only provide incremental knowledge and would not change the current recommendations.

1. Introduction and purpose

Mobile technology and smart wearable devices have changed the way we live and have become indispensable tools in many aspects of our daily activities, from navigation and communication to education and entertainment. This technical revolution has reached health applications and medicine, including neurology [1–3]. In the field of epilepsy, most research and development of wearables has been focused on automated seizure detection using non-invasive devices. Numerous survey studies have demonstrated that people with epilepsy, as well as their caregivers, need such devices [4–8], for preventing or reducing morbidity and

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mortality associated with seizures, and for objective quantification of seizure frequency and severity [9–11].

Real-time alarms, triggered by seizure detection devices, are needed for safety and prevention to decrease seizure-related morbidity and mortality. This is especially the case for tonic-clonic seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures). More than half of the patients with tonic-clonic seizures experience yearly accidental injuries related to their seizures, and 25% of them experience a serious injury requiring hospitalization, surgical intervention, or resulting in incapacitation [12]. The odds ratio for injuries is 3.5 times higher in patients with five or more tonic-clonic seizures per year, compared with patients who only have one seizure per year [12]. Tonic-clonic seizures constitute the major risk factor for Sudden Unexpected Death in Epilepsy Patients (SUDEP). All SUDEP cases documented with video-EEG occurred after a tonic-clonic seizure [13]. Experiencing tonic-clonic seizures during the preceding year was associated with a 27-fold increase in the risk of SUDEP, while no increased risk was found in patients with other seizure types [14]. Patients with at least one tonic-clonic seizure per year who do not share a bedroom have a 67-fold increased risk of SUDEP [14], the risk increasing with the frequency of tonic-clonic seizures [15].

Patients are often unable to recall their seizures, and the degree of recall can show strong intra-individual variance over time [16]. Both under- and over-reporting may occur, and the inaccurate documentation of seizure frequency affects therapeutic decisions in daily clinical practice, questioning the reliability of large drug studies, which are typically based on patient-reported seizure frequency [9]. Studies in the Epilepsy Monitoring Units (EMU), where the gold standard for seizure frequency was available from video-electroencephalogram (EEG) recordings, showed that fewer than half of the patients provided complete seizure reports, and fewer than half of all objectively detected seizures were reported [9]. This was mainly the case for focal impaired awareness seizures (73% unreported) and tonic-clonic seizures (42% unreported) [17]. Impaired recall of seizures was mainly found for nocturnal seizures (86%) but occurred even in daytime seizures (32%) [17]. An objective quantification of seizure frequency and severity is needed for fine-tuning medication tailored to the individual patient and for reliable evaluation of therapeutic interventions [9,11].

The aim of our review is to provide a state-of-the-art on automated seizure detection using non-invasive wearable devices in an ambulatory (home) environment and to highlight the prospects for future research.

2. Methods

A joint working group of the International League Against Epilepsy (ILAE) and the International Federation of Clinical Neurophysiology (IFCN) has recently published a clinical practice guideline on automated seizure detection using wearable devices [18,19]. The joint working group did a systematic review of the evidence, including papers published before October 16, 2019 (date of last search).

Here we updated the systematic literature search in PubMed for the period since the last search by the joint working group, including articles published from October 2019 until August 2023, by using the same search string as used by the ILAE-IFCN working group: ((automated detection) OR (algorithm AND detection) OR (wearable AND detection)) AND (epilepsy OR seizure).

Similarly, for the joint working group, we did a systematic review of the updated evidence and selected studies published in peer-reviewed journals, qualifying minimally as phase 2 clinical validation trials, in accordance with standards for testing and validation of seizure detection devices [20]. By adapting the key domains of the QUADAS-2 tool (quality assessment of diagnostic accuracy studies) [21] to the specific application of seizure detection devices, standards for clinical validation studies have been proposed [20]. The key features are as follows: patient selection (subjects), recording devices, flow of analysis and alarms, and reference standard. For each of these features, study designs with decreasing levels of potential bias have been listed. Using these features, five phases (0–4) have been proposed, similar to drug trials, where phase-3 studies provide compelling evidence about the accuracy of the seizure detection device, and phase-4 studies are open-label, in-field studies, in the home environment of the patients [20]. To qualify for phase 3, the clinical validation study must be prospective, multicenter, enrolling at least 20 patients with at least 30 seizures (assuming a detection sensitivity over 95%), using a pre-defined algorithm and detection-threshold, continuously running in real-time on the dedicated wearable device, and comparing the detections with the reference standard from video or video-EEG recordings [20]. The requirements for phase 2 studies are less strict, but the use of a dedicated seizure detection device is needed, and its safety has to be addressed. Retrospective analysis and using the same dataset for training and validation are still allowed at this phase. The number of patients with seizures needs to be ten or more, including at least 15 seizures in the analysis. There is a strict need for a reference standard [20].

Phases 3 and 4 studies were previously categorized by the ILAE-IFCN guideline working group as "high level" evidence in GRADE terms, while phase 2 studies were categorized as "moderate evidence". In this review paper, we followed the same principles. In this review paper, we summarize and cite all phases 3 and 4 studies published since the clinical practice guideline. Phase-2 studies, per definition, would not change the recommendation in the guideline, and the detailed description of all phase-2 studies was beyond the limitations of this paper. However, we describe selected phase-2 studies, which, in our opinion, are likely to lead to further significant development in the future. Phase-2 studies addressing modalities and detection strategies that were reported in phase-3 studies were not described in this paper to avoid redundancy.

3. Results

The ILAE-IFCN joint working group's search in October 2019 gave 1,750 studies, of which only 28 were phases 2–4. High-level evidence (phases 3 and 4) was only available for the detection of tonic-clonic seizures using wearable devices based on accelerometry, surface electromyography (EMG), or a multimodal device combining accelerometry and heart rate (Table-1). The sensitivity of these devices for detecting tonic-clonic seizures was between 90% and 96%, with a false alarm rate of 0.20–0.67 per 24 hours (0–0.03 per night). A phase-4 study showed that the use of a wearable device in the home environment of the patients helped decrease injuries related to tonic-clonic seizures in 44% of the patients, alerting for seizures that otherwise would have remained unnoticed in 55% of the patients [22]. For other seizure types, only phase 2 studies were found: using noninvasive devices, sensitivity >90% was achieved using heart rate and heart rate variability [23,24]. The high sensitivity was at the cost of frequent false alarms (up to 500 false alarms per day).

By updating the systematic literature search from October 2019 until August 2023, we further found two phase-4 studies assessing the performance of wearable seizure detection devices in a home setting [32,33]. Westrhenen et al., 2023 [32] demonstrated high sensitivity (100% median per participant) with a false alarm rate at 0.04 per h (median per patient) for nocturnal motor seizures

in children, using a multimodal device including accelerometry and heart rate detection (NightWatch), reducing caregiver stress but not showing a significant effect on the quality of life (QoL) or sleep of the caregivers. Hadady et al., 2022 [33] based their study on an online questionnaire including a high number of users who had real-world experience with using wearable seizure detection devices in their home environment. This study showed overall user satisfaction with their respective wearable device (different devices), as well as improved QoL. Most users experienced seizure detection sensitivity that was close to what previous validation studies had shown, as well as a relatively low false alarm rate (0–0.43 per day). Overall satisfaction, perceived sensitivity, and improvement in QoL were significantly higher amongst participants using validated devices (Empatica, Epi-Care, and NightWatch). Most of the patients wearing a device had tonic-clonic seizures (87%). One-third of people with epilepsy experienced fewer seizure-related injuries, and two-thirds experienced improvements in the accuracy of seizure diaries as a result of using a detection device. Besides the aforementioned studies, we found two other studies [34,35] addressing device performance and/or user satisfaction in the home environment, though they did not fulfill the criteria for a phase 4 study. Macea et al., 2023 [34] evaluated focal seizure detection based on behind-the-ear EEG, with low sensitivity (23%) and high false alarm rates (7.8% per h), on a relatively small number of patients (n = 16), thus not qualifying as a phase 4 study. The in-hospital part of the study qualifies as a phase 2 study (16 patients, 21 seizures), also presenting low sensitivity (52%), and high false alarm rates (7% per h). According to user evaluation, the likelihood of using the device in 6 months' time was 62%, mostly due to side effects and low performance. Engelgeer et al., 2022 [35] presented an economic evaluation of a multimodal seizure detection device (NightWatch), showing that device usage saves costs and reduces stress, suggesting this device is a cost-effective addition to current standard care for children with refractory epilepsy living at home. This study had a primarily economic focus and did not assess device performance regarding seizure quantification or other aspects of utility and usability, thus not qualifying as a phase 4 study.

We found four phase-3 studies and 24 phase-2 studies, published after the previous systematic review by the ILAE-IFCN working group. All phase-3 studies (Table 1) have comparable results. One phase-3 study included a large number of patients (n = 152; 85 pediatric, 67 adults) and detected tonic-clonic seizures using a multimodal device, combining accelerometry with electrodermal activity [28]. Lazeron et al., 2022 [30] used a multimodal device with heart rate detection and accelerometry to assess the detection of nocturnal major motor seizures in children with epilepsy and intellectual disability. The high false alarm rate seen in children in their study, as well as in a previous study [26], was largely due to the heart rate part of the algorithm. By optimizing the algorithm (the alarm was triggered only when the patient was in a horizontal position), they succeeded in reducing the false alarm rate by 60% (from 0.2 per h to 0.08 per h), but not at the expense of sensitivity, which remained roughly the same and comparable to that validated in the adult population [26]. Another phase 3 study [31] used audio–video analysis for automated real-time seizure detection and showed high sensitivity (93.7%) for nocturnal major motor seizures, especially tonic-clonic seizures (100%), which makes it suitable for nocturnal surveillance, allowing rapid intervention. While the majority of phase-3 trials have investigated the detection of major motor seizures, there was one prospective phase-3 study that assessed the detection of absence seizures with a wearable, single-channel EEG headband, including automated behavioral testing [29]. Their results show an average sensitivity of 78.8% (median 92.9%), and although they saw a relatively high false alarm rate (0.53 per h), the majority of patients did not experience any false alarms at all.

Even though most studies published on seizure detection devices do not fulfill the criteria for phase 3 or 4 studies, there are several that show promising results using various modalities: accelerometry combination with either photoplethysmography [36] or electrodermal activity [37], photoplethysmography alone [38], ECG [39–41], heart rate variability [42,43], behind-the-ears EEG alone [44,45] and in combined with ECG [46,47], and automated video analysis [48,49]. Phase-2 studies addressed the quantification of seizure burden using an automated approach based on EMG combined with accelerometry in patients with progressive myoclonic epilepsy [50] and a semiautomated method for quantifying the burden of absence seizures using behind-the-ears EEG [51]. An algorithm based on heart rate and oxygen saturation achieved good results (sensitivity of 87%) [52]. However, the input was based on conventional measurements and not a dedicated wearable device. A study by Frankel et al., 2021 [53] shows potential for identifying focal-onset seizures, with experts blindly reviewing data collected from a miniature, wireless, wearable EEG sensor. Furthermore, a unique study by Chen et al., 2023 [54] showed a more favorable performance of a multimodal detection platform in detecting neonatal seizures by combining data from the ECG, respiration, and accelerometer than compared to data from a single modality. Unfortunately, the number of neonates experiencing seizures was small (4 patients, 30 seizures), which might have resulted in a low sensitivity value (40%). Another noteworthy proof-of-concept study by Jeppesen et al., 2023 (phase 1 study) [55] presents an automated seizure detection method using a subcutaneously implantable cardiac monitor. They demonstrate a high sensitivity (92.6%) in detecting focal seizures with autonomic ictal changes. One recent pilot study [56] assessed out-of-hospital detection of focal impaired awareness seizures with a motor component using a multimodal approach (ECG, accelerometry, and behind-the-ear EEG). The study included 17 patients with focal impaired awareness motor seizures, with results showing sensitivity at 91% but a high false alarm rate of 18/24 h. Another study evaluated how different modalities correlate with different types of seizures [57]. Cluster analysis showed trends of greatest elevation of heart rate (HR) and accelerometry (ACC) in bilateral tonic-clonic seizures (BTCs), compared to non-BTCs and isolated auras. HR and ACC were independent predictors for overall seizure types (BTCs and non-BTCs), whereas only HR was a predictor for isolated auras. Diagnostic performance, including sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve of the predictive model for overall seizures, was 77.78%, 60%, and 0.696 (95% confidence interval = 0.628–0.764), respectively. A study by Halimeh et al., 2023 [58] showed that using prolonged postictal data (increased levels of electrodermal activity and heart rate long after seizure EEG onset) segments for seizure logging can contribute to algorithm explainability and point to influencing factors such as high antiseizure medication (ASM) dose and short seizure duration.

4. Discussion

More than twelve thousand papers have been published on seizure detection. However, most of them are strongly affected by numerous sources of potential bias, providing a too-optimistic perspective, which has caused much confusion in this field. In part, this was due to a lack of standards for clinical validation studies of seizure detection devices. By applying the standards for clinical validation studies [20], potential bias can be reduced, and the quality of the continuously growing number of studies in this field can be assessed and compared.

Table 1
Seizure detection devices validated in phase-3 clinical studies.

Study	Modality	Number of patients / number of seizures	Sensitivity	FAR	Detection latency
Beniczky et al., 2013 [25]	Accelerometry	73 / 39	90% for TCS	0.2/day	55 seconds
Arends et al., 2018 [26]	Accelerometry & heart rate	28 / 377	81% for TCS	0.03/night	Not determined
Beniczky et al., 2018 [27]	Surface electromyography	71 / 32	94% for TCS	0.7 / day (0.01 / night)	9 seconds
Onorati et al., 2021* [28]	Accelerometry & electrodermal activity	152 / 36	Children: 92% Adults: 94%, for TCS.	Children: 1.26/day Adults: 0.57/day. None during rest periods.	37 seconds
Japaridze et al., 2022* [29]	Wearable EEG-headband	39 / 364 absence seizures	average 78.8% median 92.9%, for absence seizures	0.53/h	5 seconds
Lazeron et al., 2022* [30]	Accelerometry & heart rate	23 / 1710	Before adjustment: 79.9% After: 79.4% for TCS	Before adjustment: 0.2/h After: 0.08/h	7 seconds
Armand Larsen et al., 2022* [31]	Audio-video system	191 / 16 major motor sz + 336 minor motor sz	TCS 100% HMS 80% MMS 8.3%	0.16/h	Not reported

* Published after the ILAE-IFCN guideline. TCS – tonic-clonic seizures (incl. generalized and focal to bilateral); HMS – hypermotor seizures; MMS – minor motor seizures.

Whereas real-time alarms are needed for safety indications (immediate intervention to decrease morbidity and mortality associated with seizures), offline (post hoc) analysis or a semi-automated approach can be used for seizure burden quantification [28,51,59,60]. This means that the intent of use of the seizure detection device defines its mode of operation (real-time alarm vs. offline processing).

Using the GRADE method [61,62], the ILAE-IFCN working group developed a clinical practice guideline on automated seizure detection using wearable devices, which has been endorsed by both societies [18,19]. It recommends "using clinically validated wearable devices for automated detection of tonic-clonic seizures when significant safety concerns exist, especially in unsupervised patients who do not share a bedroom but where alarms can result in rapid intervention within 5 minutes".

The recommendation was conditional, restricted to a single indication (safety), and only for tonic-clonic seizures. The working group considered that the published evidence did not justify positive recommendations for other indications (such as objective quantification of the seizure burden) and other seizure types. The guideline is expected to be updated every two years. Since then, two phase-4 studies, four phase-3 studies, and 24 phase-2 studies have been published, but they only provide incremental knowledge and would not change the current recommendations. The only area where new applications seem to be justified is the quantification of absence seizures using wearable single-channel EEG. However, only a single phase-3 study [29] supports this application, and the clinical utility of the information provided by the devices still needs to be confirmed.

There is a need for further research and development in this field. Several new approaches have the potential to solve the current impediments, namely extending the applicability of wearable devices to detecting non-convulsive seizures [63] and providing objective seizure quantification and characterization [11]. Although compelling evidence is not yet available for these approaches, they deserve more attention as they may provide breakthrough results.

Wearable EEG devices record probably the best signal type in the detection of non-convulsive seizures, yet they must be concealed to avoid stigma. This is possible using portable EEG devices with non-invasive (behind-the-ear) [29,44,45,51] or minimally invasive (subcutaneous) electrodes [64–67]. Modalities based on ictal autonomic changes (heart rate variability, electrodermal activity) may detect non-convulsive seizures, alone or in combination (multimodal devices) [24,43,55,68]. As patients may need different devices depending on their seizure types and characteristics, and some of the algorithms may need to be fine-tuned for individual patients, recording the patient́s habitual seizures might be needed in the future to tailor seizure detection for the individual patient. Selecting and fine-tuning the seizure detection device for the individual patient might be a new type of indication for doing video-EEG recording in the future.

Objective seizure quantification is challenging because it requires a high precision of seizure identification. This has not yet been achieved with the currently available devices: although they have high sensitivity (for detecting tonic-clonic seizures), the relatively high number of false alarms precludes using them for seizure quantification. Therefore, new strategies have been considered. As opposed to seizure alarms, quantification does not need real-time analysis. Off-line (post hoc) analysis allows the use of powerful cloud computing and artificial intelligence [59], and alternative detection-threshold values (different from alarm thresholds) [28], which can potentially increase precision. It also allows the use of a hybrid (semi-automated) approach, where experts review the epochs marked as potential seizures by the algorithm [51,60]. This way, experts ensure high accuracy, and algorithms minimize the workload.

In conclusion, at present, the published literature supports the use of wearable devices for automated seizure detection in patients with tonic-clonic seizures for safety indications, as specified in the clinical practice guidelines issued by the ILAE and IFCN. Further research and development are needed for other seizure types and indications.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109486.

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