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Review

Status epilepticus prevention, ambulatory monitoring, early seizure detection and prediction in at-risk patients

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ABSTRACT

Purpose: Status epilepticus is an often apparently randomly occurring, life-threatening medical emergency which affects the quality of life in patients with epilepsy and their families. The purpose of this review is to summarize information on ambulatory seizure detection, seizure prediction, and status epilepticus prevention.
Method: Narrative review.
Results: Seizure detection devices are currently under investigation with regards to utility and feasibility in the detection of isolated seizures, mainly in adult patients with generalized tonic-clonic seizures, in long-term epilepsy monitoring units, and occasionally in the outpatient setting. Detection modalities include accelerometry, electrocardiogram, electrodermal activity, electroencephalogram, mattress sensors, surface electromyography, video detection systems, gyroscope, peripheral temperature, photoplethysmography, and respiratory sensors, among others. Initial detection results are promising, and improve even further, when several modalities are combined. Some portable devices have already been U.S. FDA approved to detect specific seizures. Improved seizure prediction may be attainable in the future given that epileptic seizure occurrence follows complex patient-specific non-random patterns. The combination of multimodal monitoring devices, big data sets, and machine learning may enhance patient-specific detection and predictive algorithms. The integration of these technological advances and novel approaches into closed-loop warning and treatment systems in the ambulatory setting may help detect seizures sooner, and tentatively prevent status epilepticus in the future.
Conclusions: Ambulatory monitoring systems are being developed to improve seizure detection and the quality of life in patients with epilepsy and their families.

1. Introduction

Status epilepticus (SE) is a time-sensitive and life-threatening medical emergency. The occurrence of seizures and SE appears often random and difficult to predict, reducing the quality of life in patients with epilepsy and their families [1]. Here, we summarize the literature on ambulatory seizure detection (focusing on detection modalities and devices for ambulatory monitoring), seizure prediction (focusing on patterns of epileptic seizure and SE occurrence as well as EEG features), and tentatively SE prevention (using closed-loop warning and treatment systems in the future).

2. Seizure detection

2.1. Ambulatory monitoring systems

There are no specific articles focusing on devices for ambulatory monitoring of SE. Most devices are under investigation and, as such, have been mostly tested for detection of isolated seizures, mainly in adult patients, with generalized tonic-clonic seizures (GTCS), in long-term epilepsy monitoring units and small outpatient setting populations. A variety of modalities are used to detect seizures, such as accelerometry (ACM), electrocardiogram (EKG), electrodermal activity

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(EDA), electroencephalogram (EEG), mattress sensors, surface electromyography (sEMG), video detection systems, gyroscope, peripheral temperature, photoplethysmography, and respiratory sensors, among others.

2.1.1. Accelerometry

Accelerometry (ACM) detects changes in velocity and direction, and has been used mainly for detection of seizures with a motor component [2–5]. A frequent challenge is to differentiate seizures from daily, repetitive, rhythmic movements [3,5,6]. In addition to GTCS, ACM may also have the potential to detect focal seizures with minimal motor components, unilateral as well as bilateral tonic-clonic, myoclonic, clonic, tonic and hypermotor seizures [2–5,7–10]. Sensitivity ranges between 16–100% depending on seizure type and detection algorithm, and one study had a false detection rate (FDR) of 0.2/day [2,3,6,8–13]. Some advantages include relatively low power consumption and good patient tolerance [10–13]. One group validated a single wrist-worn accelerometer sensor and found a detection sensitivity for GTCS of 95.2% and a FDR of 0.72/day [14]. Another recent study using ACM to detect GTCS with spectral analysis had better results than the one that used temporal signal analysis achieving a sensitivity of 100% and a FDR of 2.0/day [15]. Additionally, one study validated the system in a home environment detecting 78.5% of seizures reported by parents, with 0.6 false alarms per night [12].

Disadvantages may include restriction to seizures with a motor component, and missed seizures when an obstacle limits free limb movement [2]. This modality has good sensitivity, with good night detection rates, and most patients and families found the device user-friendly [2,3,9].

2.1.2. Electrocardiogram

Electrocardiogram (EKG) can be recorded from a single channel and has a higher signal-to-noise ratio than electroencephalogram (EEG) [16,17]. The pattern of heart rate changes during seizures is highly patient-specific, warranting the development of patient-tailored detection algorithms [18–22]. EKG has been used to detect focal seizures, focal seizures evolving into bilateral tonic-clonic seizures, and GTCS [23,24]. Sensitivities in these seizure types ranged from 90% to 100% [24]. A comparison among hospital EKG, a wearable EKG device, and photoplethysmography in patients with temporal seizures in hospital setting showed sensitivities of 57%, 70% and 32%, respectively [25]. Regarding ambulatory application of EKG monitoring, a group developed a wireless EKG device with a sensitivity of 99.8% and positive predictive value (PPV) of 99.8% [26]. Cardiac-based activation vagus nerve stimulation (VNS) is now part of a commercially available closed-loop system, which reports a sensitivity of 80% [27]. The effect on seizure frequency was moderate but there was significant improvement in quality of life [27].

Some EKG disadvantages include low specificity of heart rate changes, limited stability of externally applied electrodes, and discomfort with long-term use, which could be avoided with wireless, or VNS activated devices [19,28]. Automated seizure detection from a single EKG lead is feasible, especially when parameters are tailored to the individual patient, and results improve when combined with other detection modalities.

2.1.3. Electrodermal activity

Changes in skin conductance are referred to as electrodermal activity (EDA). EDA is best detected in close proximity to sweat glands (and usually best detected in the volar surfaces of the fingers and palm of the hand) [29]. EDA reflects the activity of the sympathetic branch of the autonomic nervous system, and it may be transiently increased during epileptic seizures [30,31], specifically during GTCS and focal seizures with impaired awareness [31]. In a study including seven patients with GTCS and focal seizures with impaired awareness, EDA was significantly elevated immediately after the onset of each EEG seizure [31]. Change in EDA remained higher for longer periods of time in GTCS compared to focal seizures with impaired awareness [31]. In a study including 11 patients, 100% of GTCS were associated with a greater than 2 standard deviation increase from baseline in EDA, and up to 86% of focal seizures with impaired awareness had EDA changes [32]. EDA recordings may also add the understanding of the pathophysiology of sudden unexpected death in epilepsy (SUDEP) [32,33]. Novel frameworks are under investigation to improve processing of EDA signals [34]. There are also suggestions to utilize EDA signals in closed-loop biofeedback training, which may have the potential to reduce seizure frequency in patients with temporal seizures [35,36].

Disadvantages of EDA include susceptibility to pressure and motion artifacts, variability with temperature, and in selected patients, discomfort [30]. Larger studies on continuous ambulatory autonomic monitoring may provide additional insights to optimize this modality.

2.1.4. Electroencephalogram

Video-EEG is the gold standard for the diagnosis of epilepsy. Seizures detected with a traditional ambulatory video-EEG include a wide semiological variety, such as focal seizures with retained awareness, focal seizures with impaired awareness, focal seizures with evolution into bilateral tonic-clonic features, absence seizures [37], among others.

With the aim to facilitate portability and patients' comfort, one group developed an ambulatory noninvasive EEG monitoring device with 2 channels connected via Bluetooth to a smartphone [38]. The device was tried in 3 patients achieving a detection sensitivity of 75–100% [38]. Another noninvasive 2-electrode EEG monitoring device is able to track seizures for seven days and allows home monitoring [39]. Finally, as part of the efforts to simplify EEG recordings and make interpretation easier, another group developed a portable EEG data recorder and a noninvasive 10-electrode headband with rapid setup (approximately 5 min). This device was compared to a commercially available EEG widely used in clinical setting showing similar signal quality, while requiring less setup time and allowing greater portability [40,41].

Intracranial EEG (iEEG) offers advantages of better localized signals and decreased biological noise [42]. Some implantable intracranial devices based on iEEG are detailed in the subsection 4.1 [43,44]. Recently, a multicenter collaboration that worked on high quality intracranial data achieved robust and accurate seizure detection [45]. The development of new prediction methods, mainly based on iEEG data, has yielded prediction accuracies of 75.8–97.5%, and false prediction rates of 0.05–1/h [46–56].

Potential disadvantages of noninvasive EEG may include that patients often have to wear scalp electrodes and remain attached to EEG equipment, which is uncomfortable, may increase artifacts and may lead to stigmatization, as electrodes are often difficult to hide [57]. However, in the future, these challenges may be overcome by lighter and smaller monitoring systems, which may also be implanted subcutaneously or in the subgaleal space in selected cases. Limitations of iEEG include risks associated with a surgical procedure as well as those of wearing an implanted device.

2.1.5. Mattress sensors

Mattress sensors are usually placed under the patient's mattress or bedding, and connected to a monitor. The sensor alerts the caregivers when a stimulus above the selected threshold is detected [58–60]. These sensors use detection techniques based on pressure changes triggered by patient's movement. Nevertheless, novel sensors may be able to detect air-pressure fluctuations caused by the tiny tremors of heartbeats –heart rate and breathing can be tracked and apneas may already be detected-. The seizures detected with classic mattress sensors are GTCS and focal seizures with impaired awareness and motor onset. The reported sensitivity of three devices ranged from 16.7% to 85%, being better for nocturnal GTCS [58–60]. Monitoring while the patient

is in bed may be helpful, as most cases of SUDEP occur in patients with GTCS, while unsupervised, in bed at night [61,62]. Furthermore, mattress sensors do not require device attachment to the patient's body.

These devices have the disadvantages of currently having weight restrictions, detecting only seizures with rhythmic movements, and often have relatively low sensitivity [59,60]. Individual calibration and testing over a couple of nights in a home setting may be helpful, and might improve sensitivity [58].

2.1.6. Surface electromyography

Analysis of muscle activity with sEMG is a viable option for seizure detection, mainly for seizures with a motor component [63]. sEMG detects muscle activity with one channel [64–66]. sEMG during tonic seizures, recorded over the deltoid muscle, had a sensitivity of 53–63% and a FDR of 1.49–4.03/h, achieving better results when certain parameters were tailored for each patient [63]. sEMG electrodes placed on the biceps and triceps detected 95% of GTCS, with only one false positive, during a recording period of 1399 h, but no other seizure types (myoclonic, tonic, absence, and focal seizures with or without loss of awareness) were detected [67]. An EMG-based system well-placed over the belly of the biceps demonstrated 100% sensitivity to detect GTCS (n = 29 episodes) when compared with video-EEG, with a detection delay average of 7.7 s from the onset of bilateral appendicular tonic motor manifestations, and a mean false alarm rate of 1.4/24 h [68]. This system has a web-portal that allows to view detection times, and adjustment of detection settings [68]. In another similar blinded study including 71 patients, this device had a sensitivity of 93.8% (30 out of 32 GTCS), a median detection latency from the tonic phase onset of 9 s, and a false alarm rate of 0.67/24 h [69].

Disadvantages of sEMG sensors may include discomfort and irritation when attached to the skin. As with other sensors, there may also be potential for detachment [66–68]. Better results may be achieved when certain parameters are tailored to the individual patient, in particular for tonic seizures [63]. Therefore, sEMG reliably detects GTCS and tonic seizures, and could potentially detect other seizure types with a motor component [69].

2.1.7. Video detection systems

Automatic video detection systems use video-based fiducials as well as area, duration, velocity, rotation, oscillation, angular speed, and/or motion trajectory to detect seizures [70–74]. The systems are classified as marker-based or marker-free, depending on whether the cameras track detectable markers placed in determined sites [70]. Seizure types that can be captured by video include focal, hypermotor, myoclonic, and clonic [70–72,75], and tentatively in the future other seizure types with more complex motor or automotor features, prominent behavioral arrest, and depending on camera features, seizures with skin color or skin temperature changes, as well as respiratory and heart rate changes, among others. Current sensitivity varies from 75 to 100%, with a PPV over 85%, and a specificity of 53–93% [70–73]. A video monitoring system in a residential care unit facilitated nocturnal surveillance; in fact, 33% of all observed seizures were only seen on video, including mainly tonic seizures [76]. However, video monitoring was costly, and without further data processing was not recommended for broad implementation [76].

The main disadvantage in marker-based video detection devices is that sensors can be uncomfortable or dislocate with prolonged use [71,74]. Marker-free systems to date are limited to detection of seizures with a motor component, and they are also more limited to the area covered by video: the patient must be visible and natural fiducials may need to be on camera [70]. Seizure detection based on video is feasible, but currently, this may recognize seizures with major movements best.

2.1.8. Other potential future modalities

A state in which seizure occurrence is highly likely must be identified to forecast seizures. Several biophysical or metabolic parameters could be measured to help determine this, and in combination with the modalities mentioned, may achieve optimal seizure detection, and even prediction. Some parameters seem to change during or prior seizures, such as ionic changes in vivo -for example extracellular potassium levels-, pH, oxygen, very fast oscillations, and intracellular NADH/FAD + [77]. In addition, cortisol, mood, orexin, temperature, respiration, sex hormones, glucose, inflammatory markers, time of day, blood oxygen, ketones, among others, have also been proposed as parameters that could enhance a seizure forecasting algorithm [78]. Devices to monitor these potential biomarkers are currently being developed and refined [79,80].

2.2. Combination of detection modalities

Multimodal seizure detection devices may have advantages over uni-modal systems, since combination of modalities may at times achieve higher sensitivities with lower FDR [81]. Some available multimodal signal combinations have been tested in selected studies, and may be useful in SE detection and prevention.

2.2.1. Accelerometry and electrodermal activity

The combination of EDA and ACM offers improvement in the detection of motor seizures and selected seizures with autonomic involvement, with a potential role in SUDEP risk evaluation and prevention. Wrist-worn devices were used to record EDA and ACM from 69 patients at 6 clinical sites, obtaining 5928 h of data, including 55 convulsive seizures from 22 patients [82]. Three automatic classifiers were then used to detect seizures, and all detected seizures prior to video EEG onset, with comparable latencies [82]. One classifier had a sensitivity of 94.5%, and a false alarm rate of 0.2 events per day [82]. The seizures detected were focal tonic-clonic and focal evolving into bilateral tonic-clonic seizures, and all nocturnal seizures were detected by 2 classifiers [82].

2.2.2. Accelerometry and surface electromyography

This combination was proposed since ACM seems to be more sensitive in detecting the clonic phase, and sEMG appears to have greater sensitivity to specifically detect phases of GTCS, such as the tonic phase [83]. One study in children with tonic-clonic seizures achieved a sensitivity of 91%, with a FDR of 0.5/12 h, utilizing a combination of two ACM and two sEMG sensors [83].

2.2.3. Video, accelerometry and radar induced activity (VARIA system)

This system uses video, accelerometry and radar induced activity to detect seizures based on joint movements [84]. A camera and a motion sensor (radar) are attached to a tripod placed near the patient's bed. Four sensors with 3-axis ACM and streaming wireless communication are placed on elastic bracelets, worn around wrists and ankles. A laptop stores all movement data recorded by camera, radar or ACM sensors [84]. VARIA was tested in two patients with tonic-clonic seizures in a home environment, with a sensitivity of 66.9%, and a FDR of 1.16 per night [84]. Challenges of this system may include numerous, easily removable bracelets [7], requiring potentially further refinement prior to routine and everyday monitoring application.

Facilitated by advances in device development, further work on modality combinations is in progress [81]. Table 1 summarizes the sensitivity and FDR of the detection modalities outlined above (Table 1).

2.3. Training of modalities

Individualized training of detection modalities and selection of specific sensor combinations for each patient may improve individual seizure detection rates. Regarding device selection, patient's characteristics and clinical seizure type evaluation may help select the most

Table 1
Sensitivity and false detection rate (FDR) of detection modalities.

Modality		Sensitivity	FDR
Unimodal	ACM	16–100%	0.2–2.0/day, 0.6/night
	EKG	57–100%	–
	EDA	86–100%	–
	Noninvasive 2/10-electrode EEG	75–100%	–
	Mattress sensors	16.7–85%	–
	sEMG	53–100%	1.49–4.03/h, 1/1399 h, 0.67–1.4/24 h
	Video detection systems	75–100%	–
Multimodal	ACM and EDA	94.5%	0.2/day
	ACM and sEMG	91%	0.5/12h
	Video, ACM and radar (VARIA system)	66.9%	1.16/night

Legend. ACM: accelerometry. EKG: electrocardiogram. EDA: electrodermal activity. EEG: electroencephalogram. sEMG: surface electromyography. FDR: false detection rate.

appropriate monitoring modality. Optimal detection device for selected seizure types may differ, including a combination of sensor modalities, as multimodal devices may yield better results in selected patients. For example, sEMG and EDA may serve as a viable combination for tonic seizures, EDA and EKG for focal seizures with impaired awareness and autonomic changes, and ACM and/or sEMG for myoclonic and clonic seizures.

Individualization and personalization of seizure forecasting algorithms may be necessary, including multiple additional variables. Seizure generating mechanisms and preictal dynamics might be different among patients and among different types of seizures in the same patient. There is a lot of variability in time patterns in epilepsy patients, but the same patient longitudinally often tends to present with more consistent patterns [85]. An initial training phase may be helpful to tailor the algorithm to the patient's characteristics, ictal data, and interictal data in order to develop a patient and seizure-type specific forecasting algorithm [85]. Taking all of these features into consideration might improve seizure detection and make limited seizure prediction possible.

2.4. Portable devices approved by the U.S. FDA

2.4.1. SPEAC system (Brain Sentinel)

The Brain Sentinel Monitoring and Alerting System, also known as SPEAC system, is a portable seizure detection and alerting system. SPEAC system is composed of a wireless sEMG monitor attached to a non-invasive sEMG electrode patch placed on the biceps (unimodal device). Since this device measures muscle activity, the system focuses on detection of prominent motor seizures. The system also provides audio recordings and warning alarms to caregivers when events are detected, and includes a seizure diary. Minor motor events not detected in real-time may be identified since the sEMG is recorded. This device is FDA approved to detect GTCS.

2.4.2. Embrace (Empatica)

Embrace is a wrist-worn seizure-alerting smartwatch which includes a 3-axis accelerometer, an EDA sensor, a gyroscope, and a peripheral temperature sensor. Embrace transmits data to a paired smartphone via Bluetooth, and the smartphone resends these data to Empatica servers. This system alerts caregivers when events are detected (through an Alert App), it provides a seizure diary, and tracks daily rest - physical activity (through Mate App). Convulsive seizures with rhythmic motor movements involving one or both upper and/or lower extremities may be detectable by this device. This device is FDA approved to detect GTCS.

2.4.3. Ceribell EEG system (Ceribell)

Ceribell is a noninvasive EEG system composed of a 10-electrode headband and a 'Brain Stethoscope function' which converts EEG to sound in real-time. Ceribell allows rapid access to EEG −5 min to set up-, as well as rapid and easy interpretation by listening, without requiring any epileptologist or EEG technician [41]. Its quality is equivalent to conventional EEG and may present even higher sensitivity [41]. Ceribell is able to detect any type of seizure but, since the system selects individual channels, focal seizures in other channels are not detected, and therefore it is mainly intended to detect generalized or hemispheric patterns. Its use in ED and ICU may allow earlier and easier seizure detection and to select patients who should undergo a formal EEG study for better seizure classification [41]. Ceribell is FDA approved as an EEG device.

3. Seizure prediction

3.1. Patterns of epileptic seizure and SE occurrence: big data and machine learning

Seizure occurrence appears random because seizure patterns may often be too complex to be described by any simple intuitive model, but seizures may follow complex non-random patterns [86]. There are examples of patterns of seizure occurrence [86] based on seizure onset [87–89], seizure semiology [88,90,91], seizure evolution [92,93], triggers such as hormonal factors [94] and weather variation, among others [95–98]. The pattern of seizure occurrence is most often described over a 24 h period, and may be influenced by time of day and sleep-wake stage [88,99]. However, the pattern of seizure occurrence seems to be more irregular and complex than a simple circadian pattern, as well as highly individual-specific [100,101]. Some studies suggest that patient-specific ultradian and infradian rhythms may also contribute to the distribution of seizure occurrence [101]. Regarding the pattern of SE occurrence, it may simply reflect the pattern of seizure occurrence or may have its individual and more complex distribution.

Studying complex patterns with occasional events, such as SE, requires numerous data points. This allows for the introduction of big data and machine learning in seizure detection and prediction. The increasing use of large databases –from large multicenter networks [102,103] and large patient self-reported databases [104] – and machine learning techniques may help to better define patterns of SE and seizure occurrence in individual patients, and therefore, may permit prediction [105]. Simple learning algorithms may serve as basic building blocks that lead to more advanced approaches, like deep learning and neural network approaches. The integration of learning algorithms in wearable detection device algorithms may lead to closed-loop systems for seizure detection and prediction [81]. However, if the input data is not of sufficient quality, the result may also be less than perfect ('garbage in, garbage out') [106], and machine learning may not be able to easily resolve or make up for poor data quality.

Seizure susceptibility assessment, based on simultaneously collected diary and longitudinally evaluated seizure susceptibility intervals, may also provide opportunities for chrono-pharmacological approaches [28].

3.2. EEG analysis

Cerebral electrical neuronal activity may exemplify a chaotic system, allowing for epileptic seizure description and seizure occurrence prediction through nonlinear differential equations, similarly to other dynamic systems [86,107–110]. For this reason, long-term EEG recordings may benefit from nonlinear analysis, and ultimately may provide practical tools in epilepsy care and management [110–113]. In fact, following nonlinear EEG analysis based on chaos theory, several chaotic levels depending on the epileptic state have been discovered: the ictal state corresponds to a certain degree of order, the postictal

state corresponds to chaos, and the pre-ictal state corresponds to an intermediate level between chaos and order [110]. In addition, different chaotic levels are registered from epileptogenic and non-epileptogenic areas during interictal states [110,114].

Furthermore, the relationship between some EEG features and seizure onset also supports the concept of non-randomness in brain neuronal activity. Examples of EEG features prior to seizure onset include long-term energy bursts [115], missing ordinal patterns in deterministic dynamics [116], reduction of sleep spindles [117], and subject-specific changes in spike rate [101]. Additionally, interictal epileptiform activity may also follow rhythmic patterns [118]. Moreover, focal seizures may be characterized by seizure groups of fixed duration and interval also supporting non-randomness [100]. Regarding end of seizures, self-terminating seizures seem to end through a common dynamical mechanism via a critical electrophysiological transition, in contrast to SE that does not cross the critical transition despite repeated approaches [119]. Therefore, both onset and end of seizures may be potentially predicted.

4. Status epilepticus prevention

4.1. Closed-loop detection-treatment systems

Combinations of seizure detection sensors based on EEG and extracerebral signals may be integrated into portable devices to facilitate seizure detection in ambulatory settings. The device may be able to access patients' healthcare data, and other pertinent data points. When a seizure is detected, the caregiver may be informed and this may lead to an intervention or corrective response, which could imply abortive pharmacotherapy, neurostimulation or even micro-pump systems that deliver medication, as well as acute seizure care and transport to an emergency room if needed [81]. In the future, development of closed-loop prediction, detection, and treatment systems in clinical routine may help identify and treat seizures earlier, and therefore, prevent SE reducing related morbidity and mortality [120–123].

Some implantable intracranial devices based on iEEG provided opportunities for closed-loop monitoring in patients with refractory focal epilepsy [43,44]. However, the risk of neurosurgery and of wearing an implanted device currently limits widespread application. We outline selected devices subsequently:

4.1.1. NeuroVista

This implanted advisory system, comprised of two silicon implantable leads each with eight platinum iridium contacts, was placed over the epileptogenic area in patients with refractory focal epilepsy [44]. A patient-specific algorithm was developed during data collection and the recorded EEG was analyzed by a portable device [44]. After four months in the advisory phase, the median sensitivity of seizure prediction in the high likelihood performance was 60% (10 adults) -based on correlated clinical seizures- with a median time in high advisory of 27.5%. The clinical usefulness of seizure prediction was inconclusive, mainly because of the variability in warning times and difficulties adapting to the system [44]. Nevertheless, the system was useful to detect and predict seizures in selected patients, and provided new detailed information on epileptogenic focus and previously undetected seizures [44]. Within one year after implantation, four patients among 15 had serious adverse effects, including device migration and infection [44]. While feasibility of such a system was demonstrated, reportedly funding to develop and market the system was not available, and therefore, this system is currently not available.

4.1.2. NeuroPace

This implanted device consists of a programmable neurostimulator that detects abnormal electrocorticographic activity and provides responsive cortical stimulation [43]. This system is connected to 1 or 2 recording and stimulating depth or subdural strip leads placed on the epileptogenic area, and its detection and stimulation parameters can be tailored individually [43]. In a multicenter, double-blind, randomized controlled trial (n = 191 adults), patients with refractory focal epilepsy randomized to receive stimulation in response to abnormal electrocorticographic activity presented greater reduction in seizure frequency than patients randomized to no stimulation. Furthermore, there were no differences in adverse events, and quality of life improved [43].

Efforts to improve epileptic seizure detection and prediction may positively affect SE prevention, since acute treatment may be administered earlier and chronic medication may be tailored to the individual patient (for example, using chrono-pharmacological approaches, such as differential antiepileptic dosing). As portable devices use wireless technology and batteries, signal dropout may need to be anticipated, and may represent a current shortcoming without implementation of adequate backup systems.

5. Conclusions

Seizures tend to follow complex and patient-specific distributions despite their apparently random occurrence. The combination of multimodal monitoring devices, big data sets, machine learning and other potential novel approaches –such as biomarkers at seizure prone states- may enhance patient-specific seizure forecasting algorithms and allow for an improved detection and sooner intervention. The implementation of closed-loop systems in ambulatory settings may help prevent SE in the future, and therefore, this may potentially reduce morbidity and mortality in epilepsy and ultimately improve quality of life in patients and caregivers.

Contributors

Marta Amengual-Gual, Adriana Ulate-Campos, and Tobias Loddenkemper participated in literature review, article design and outline, manuscript development, manuscript drafting, manuscript writing, and writing supervision.

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Ethics

This study complied with biomedical research ethical standards.

Declaration of interest

Marta Amengual-Gual reports no conflict of interest.

Adriana Ulate-Campos reports no disclosures.

Tobias Loddenkemper serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council (and as President) of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for Seizure, and as an Associate Editor for Wyllie's Treatment of Epilepsy 6th and 7th edition. He is part of pending patent applications to detect and predict seizures and to diagnose epilepsy. He receives research support from the Epilepsy Research Fund, the American Epilepsy Society, the Epilepsy Foundation of America, the Epilepsy Therapy Project, PCORI, the Pediatric Epilepsy Research Foundation, CURE, HHV-6 Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt and Pfizer. He serves as a consultant for Zogenix, Upsher Smith, Sunovion, Engage, and Advance Medical. He performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other

electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies including the AAN, AES and ACNS, and for grand rounds at various academic centers. His wife, Dr. Karen Stannard, is a pediatric neurologist and she performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures and she evaluates pediatric neurology patients and bills for clinical care.

The authors report no potential conflicts of interest.

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