Title: **The role of devices in managing risk**

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Abstract

Over the last few years, there has been significant expansion of wearable technologies and devices into the health sector, including for conditions such as epilepsy. Although there is significant potential to benefit patients, there is a paucity of well-conducted scientific research in order to inform patients and healthcare providers of the most appropriate technology. In addition to either directly or indirectly identifying seizure activity, the ideal device should improve quality of life and reduce the risk of SUDEP. Devices typically monitor a number of parameters including EEG, cardiac and respiratory patterns and can detect movement, changes in skin conductance and muscle activity. Multi-modal devices are emerging with improved seizure detection rates and reduced false positive alarms. Whilst convulsive seizures are reliably identified by most unimodal and multimodal devices, seizures associated with no, or minimal, movement are frequently undetected. The vast majority of current devices detect but do not actively intervene. At best, therefore, they indicate the presence of seizure activity in order to accurate ascertain true seizure frequency or facilitate intervention by others, which may, nevertheless, impact on the rate of SUDEP. Future devices are likely to both detect and intervene within an autonomous closed-loop system tailored to the individual and by self-learning from the analysis of patient-specific parameters. The formulation of standards for regulatory bodies to validate seizure detection devices is also of paramount importance in order to confidently ascertain the performance of a device and this will be facilitated by the creation of a large, open, database containing multi-modal annotated data in order to test device algorithms.

Keywords

SUDEP

Medical devices

Wearable technology

Epilepsy

Abstract word count: 259

Word count: 4655

1. Introduction

Whilst devices, and particularly wearable technology, have been commonplace in the entertainment, navigation, education and communication industries, there is now significant expansion into the health sector. Technological advances have facilitated the development of portable, reliable and effective devices which are becoming more widely accepted and utilised in the management of a number of health conditions, including epilepsy.

The potential for devices to assist in managing risk in epilepsy is significant but the technologies are varied, frequently complex, inconsistently validated and potentially confusing, not only for people with epilepsy but also their friends, families and healthcare providers.

The lack of robust scientific evidence creates a vacuum readily filled by commercially driven claims and reassurances and this is a challenging environment for patients, families and carers to choose a suitable device ideal for their needs. Importantly, the source of funding for studies, validity of data and implications of both true and false positive alarms needs to be transparent. Furthermore, it is mandatory that over-reliance on seizure alert devices is avoided and they are considered to be only one part of the holistic management of seizure disorders.

The ideal device for seizure disorders should detect and abort pre-ictal or ictal epileptic activity thereby reducing seizure frequency and severity, but also monitor and reduce cardiorespiratory impact and autonomic dysfunction, provide a pre-ictal warning, summon assistance if required and store biometric data for later interrogation and integration. Devices should also be safe, easy to use, comfortable and unobtrusive[1, 2]. Finally, of principal importance, devices should have an impact on the risks associated with seizures, including sudden unexpected death in epilepsy (SUDEP).

To date, all of these characteristics do not exist in a single device, but the integration of seizure detection and intervention remains an important therapeutic goal and it is very likely that reliable and validated devices in this regard will begin to emerge over the next 10 years.

In contrast to the rapid technological advances, the scientific evidence for the diagnostic utility of wearable devices is limited and this is a significant impediment to their integration into rational medical decision-making. A Cochrane review, undertaken in 2016, evaluated the quality of the evidence regarding treatments for the prevention of SUDEP, including seizure detection devices. The review highlighted a deficiency in the literature base on the effectiveness of a wide range of interventions to prevent SUDEP, and noted that whilst devices have varying sensitivities in their capacity to detect seizures, this is not synonymous with lowering SUDEP risk[3]. Nevertheless, early seizure detection, or the disclosure of previously undetected seizure activity, for example nocturnal events, is very likely to be fundamental in managing some, but not all, risks associated with epilepsy.

Early and accurate detection of seizures is likely to lead to earlier acute intervention and better informed long-term seizure management, which may, in turn, result in a lower SUDEP rate. In this regard, a number of devices perform adequately with high sensitivities for convulsive and other motor seizures, and low false detection rates which is important in managing alarm fatigue. Multimodal devices, with improved seizure detection rates and usability, are now commercially available and with advances in wearable technology these are likely to become commonplace.

The detection of seizure activity may be direct, through real-time interrogation of electroencephalographic (EEG) recordings or indirect, by monitoring other parameters such as cardiorespiratory function, movement, muscle activity or skin conductance.

2. Direct seizure detection and intervention

The evaluation of real-time EEG data is ideal[4], and necessary, in order to meaningfully intervene. The acquisition of continuous scalp EEG monitoring data is however, at best, obtrusive, temporary and uncomfortable[5]. This may change, however, with the development of subcutaneous EEG electrodes[6]. Conversely, whilst the implantation of intracranial EEG monitoring devices is convenient, there is an inherent risk of surgical complications and enduring post-operative morbidity[7]. One advantage of continuous EEG monitoring is the potential to identify pre- or early ictal changes. This may facilitate intervention at a pre-symptomatic stage which may be user-independent, for example, with the responsive neurostimulation devices[8] or provide advisory warnings to enable the individual to undertake precautionary measures[7]. A study of responsive cortical stimulation demonstrated a 37.9% reduction in mean seizure frequency in the treatment group compared with a 17.3% reduction in the sham group. During the study, seven deaths were attributed to SUDEP, three of whom were in the stimulation group. The rate of probable or definite SUDEP for implanted participants was 3.5 per 1000 patient implant years (confidence interval 1.5-8.5) and 2.6 per 1000 patient stimulation years (confidence interval 1.0-7.0). The seven SUDEP deaths over the 340 patient-years (11.8/1000 patient-years) is considered to be within the expected range for this refractory population[9]. The study was primarily conducted to evaluated seizure control and not SUDEP risk and the potential impact of open and closed loop EEG systems on SUDEP rates is uncertain. There is a clear reduction in seizure frequency with stimulation in some patients but the seizure freedom rate, a key factor with respect to SUDEP, was relatively low, with 12.9% of patients with responsive direct neurostimulation having at least a one-year period of seizure freedom but no patients were seizure free for the entire follow-up period of a mean of 5.4 years[9]. Other forms of neuromodulation besides direct electrical stimulation are currently being evaluated including optogenetics[10] and local drug delivery systems[11].

It has long been considered that, whilst seizures are largely unpredictable, a number of patients may experience prodromal behavioural or cognitive changes several hours before clinically evident seizure activity emerges, and this concurs with experimental evidence of cortical hyperexcitability[12]. On this basis, a long-term intracranial seizure advisory system has been trialled in a small number of patients. A hand-held device received and analysed 16-channel intracranial EEG data and displayed the likelihood of experiencing a seizure in the minutes or hours ahead. The implantable telemetry unit only received EEG data; no stimulation was administered, unlike the closed-loop responsive neurostimulation devices[7]. In the 15 patients studied, 4 experienced serious adverse events such as infection or device migration. The mean sensitivity of predicting a “high chance” of a seizure was 66% and the mean warning time was 114 minutes, with a range of 5-960 minutes. For some patients, particularly those with only rare “high chance” periods, this information was useful in planning activities or warning others of impending events. Further developments are likely to concentrate on improving the prediction algorithm and providing a mechanism to intervene once pre-ictal activity is detected.

In addition to behavioural change, the varying hour-by-hour risk of seizures also raises the possibility of chronotherapy, which can be defined as tailored therapeutic intervention based on time-varying seizure risk[13]. Short-acting anti-epileptic medication or neurostimulation can be more effectively targeted to periods associated with the highest risk and medication may be able to be moderated at other times, reducing both adverse effects and medication tolerance or dependence.

3. Indirect seizure detection and intervention

3.1: Autonomic

Whilst EEG recordings could be considered the optimum pre-ictal information, data acquisition is challenging and, on this basis, indirect or surrogate biomarkers have been evaluated. A pre-ictal increase in heart rate has been demonstrated in 36% of patients with temporal lobe epilepsy[14] and changes in heart rate variability have been identified in up to 70% of patients, 13.7 minutes before clinical seizure onset[15]. With recent technological advances in wearable devices monitoring cardiac function and other physiological parameters such as oxygen saturation it may be possible in future to provide patients with real-time seizure risk information with similar accuracy to the intracranial EEG recordings.

Ictal tachycardia, typically a 33-34 bpm increase, is seen in 80-90% of seizures and this is largely independent of seizure type[16]. Automated ECG seizure detection algorithms have demonstrated sensitivities of 90-98% in identifying heart rate changes in seizures associated with tachycardia[17, 18] and this can been improved with more sophisticated analyses of heart rate variability[19, 20]. The heart rate accelerates more rapidly during epileptic seizures than during physical activity or nocturnal arousals and it is on this basis that vagal nerve stimulators have been developed which incorporate a cardiac based seizure detection algorithm (CBSDA) to monitor heart rate in order to inform periods of stimulation[21]. Specifically, when the relative heart rate increases above a pre-programmed threshold for at least 1 second, a single VNS stimulation train is automatically delivered. Thirty-one patients with drug resistant epilepsy were evaluated in an epilepsy monitoring unit to assess algorithm performance and clinical benefit. Sixty-six seizures from 16 patients were available for analysis. In 37 seizures a >/= 20% heart rate increase was detected and 27 out of 66 seizures (sensitivity 41%) were stimulated within 2 minutes of seizure onset. In 10/17 of these seizures, where triggered VNS overlapped with ongoing seizure activity, seizure activity stopped during stimulation. Additionally, quality of life scores showed a significant improvement at 12 months. The false activation rate was high however, at 171.6 events per day, with a heart rate increase threshold of 20%[21]. A further study of 20 patients evaluating the cardiac AutoStim function feature of VNS (AspireSR; LivaNova) showed that 73.7% of focal impaired awareness and focal to bilateral tonic-clonic seizures were associated with an increase in heart rate of 20% or greater. The AutoStim activated during 34.8% of all seizures and in 61.3% of these, seizures ended during the stimulation phase with a median time from stimulation onset to seizure cessation of 35 seconds. This was associated with improvements in 50% responder rate, quality of life measures and seizure severity scores[22].

Ictal bradycardia and asystole is reported, albeit rarely, in patients with refractory epilepsy[23]. The potential relationship to SUDEP has not been elucidated. A permanent pacemaker is an implanted device that provides electrical stimuli, and therefore, cardiac contraction when intrinsic myocardial electrical activity is inappropriately slow or absent. There are numerous case reports of patients with epilepsy and ictal asystole receiving permanent pacemakers to prevent further episodes[23, 24] but there is also a report of a presumed, but unconfirmed, SUDEP death in a patient with a pacemaker[25]. Whilst a pacemaker may prevent the future occurrences of cardiac asystole and possibly serious morbidity secondary to falls and head trauma[26], it has not yet been established whether the implantation of a pacemaker will modify the risk of SUDEP. Additionally, the rate and significance of brief, asymptomatic bradyarrythmias and asystole in a healthy population has not been established. Specifically, the possibility that ictal asystole is a benign, self-limiting condition with characteristics similar to vasovagal syncope / asystole has been proposed, in which case, compensatory mechanisms should prevent the progression to permanent cardiac arrest, and SUDEP[27]. For cases of SUDEP associated with severe

respiratory compromise with secondary bradyarrhythmia, pacemaker implantation may not be helpful. It is impractical to undertake a controlled study on rates of SUDEP in pacemaker implanted and non-implanted patients with epilepsy due to the number of implanted patients needed to obtain a significant difference between patient groups. For cases of possible tachyarrythmia-associated SUDEP, an implantable cardioverter-defibrillator (ICD) may be more appropriate[28].

Alterations in respiration such as coughing, hyperventilation, irregular breathing, apnoea, laryngospasm, and neurogenic pulmonary oedema have been described with seizures. Some form of respiratory compromise is regularly reported in witnessed cases of SUDEP[29]. Oxygen desaturations of <90% are common, occurring in approximately one third of generalised and non-convulsive seizures and in <5% of cases these desaturations may be profound, with measured oxygen saturation of <70%[30]. Significant desaturations have also been noted in electrographic seizures without clear clinical accompaniments[31]. The MORTEMUS study group acquired cardiorespiratory data from 11 monitored cases of SUDEP[32]. There was evidence of an initial tachypnoea after a secondarily generalised tonic-clonic seizure, followed within 3 minutes by transient or terminal cardiorespiratory dysfunction. When transient, the cardiorespiratory dysfunction recurred within 11 minutes of the end of the seizure with terminal apnoea, followed by cardiac arrest. At present, there is no reliable non-invasive method to detect apnoea that is suitable for long term use in low clinical intensity or domestic environments. Pulse oximetry, for example, suffers from artefacts and false alarms, and the delay between the beginning of apnoea and detection of oxygen saturation drop limits their applicability. The first clinical study of a novel wearable apnoea detection device (WADD) which captures the acoustic signal of airflow in the trachea via a sensitive microphone and utilises noise-cancelling software, confirmed that it is able to detect apnoea even in the presence of artefacts in healthy subjects and individuals with sleep apnoea. The small device is attached to the neck with a hydrocolloid plaster of less than 3cm diameter and can remain in place for several days at a time. WADD had 99.2% sensitivity, and 99.6% specificity for detection of voluntary 15-30 second apnoea whereas the automatic software of the FDA approved ambulatory SOMNO system, comprising finger oximetry; oronasal flow sensors, thoracic and abdominal expansion bands and ECG (SOMNOmedics Gmbh) had 37.8% sensitivity and 90.5% specificity. A clinical trial in individuals with epilepsy and frequent seizures who are undergoing video-EEG telemetry with respiratory monitoring is currently underway and it is expected that some algorithm and sensor redesign will be necessary to compensate for seizure activity and make the technology highly sensitive and specific[28, 33].

Transient changes in skin conductance reflects activation of the sympathetic branch of the autonomic nervous system. Electrodermal activity (EDA) is seen during seizures, with a mean latency of 33 seconds[34]. This is particularly evident in convulsive seizures (100% detection rate, as defined by an increase in EDA of greater than two standard deviations) rather than focal impaired awareness seizures (86% detection rate)[35]. There is a strong correlation between the degree of EDA change, as a biomarker of autonomic dysfunction, and duration of post-ictal generalised EEG suppression (PGES) which is considered to be a possible pathophysiological mechanism of SUDEP[35, 36]. Furthermore, a large increment in EDA, as measured with a wrist-worn device, was seen in the immediate post-ictal period recorded from a patient who died of SUDEP as a result of the seizure, reflecting significant autonomic, predominantly sympathetic, dysfunction and possible PGES[37]. EDA recording is susceptible to motion and pressure artefacts but devices monitoring skin conductance and other parameters, including movement, on a long-term basis have been developed and tested with promising results[38].

Increased cerebral blood flow has been shown to precede the onset of temporal lobe seizures by up to 20minutes[39, 40]. Regional cerebral oxygen saturation sensors placed on each side of the forehead were able to detect pre-ictal changes in oxygen saturation, an average of 18 minutes prior to EEG seizure

onset, in 4 of 7 convulsive episodes[41]. Near-infrared spectroscopy (NIRS), typically measured using a spectrophotometer placed on the forehead, is also able to detect pre-ictal increases of cerebral oxygen saturation, of up to 7%, 5 minutes before seizure onset followed by ictal desaturation but the use of a portable detection device evaluating numerous haemodynamic parameters, including NIRS, showed a sensitivity of only 6-24% [42, 43] and this limits their usability.

3.2: Physical parameters

3.2.1: Accelerometers

Intuitively, the detection of seizures should involve some form of monitoring of movement or muscle activity. The differentiation of normal daily repetitive movements and seizure activity is challenging however and can lead to a high false alarm rate. Accelerometers detect changes in velocity by means of a three-axis motion sensor and microprocessor in a portable device typically worn on a limb. Different seizure types are associated with disparate patterns of movement. For example, a burst signature is seen with clonic seizures whereas tonic seizures are block-shaped due to constant acceleration and this makes them difficult to distinguish from slow, normal movements.

In one study, the wrist-worn device correctly identified 20 of 22 (91%) recorded tonic, clonic or tonic-clonic seizures and the alarm was activated within a median period of 17 seconds. All events lasting longer than 30 seconds were identified. There were eight false alarms during 1,692 hours of monitoring which equates to an acceptable rate of one false alarm every 9 days[44]. A multicentre study of a wrist-worn accelerometer evaluated 39 convulsive seizures in 20 patients and demonstrated a sensitivity of 90% with a false alarm rate of 0.2 per day and a mean detection latency of 55 seconds[45]. This device was investigated in the home environment and satisfactory sensitivity and false alarm rates were sustained (90% and 0.1/d). Adverse effects occurred in 11%, but were generally mild, such as skin irritation at the wrist and interference with home electronic appliances[46]. Others have reported similar findings[47], but this has not been universal. For example, in a study of one of the most popular commercially available devices which evaluates accelerometer data and issues text and phone call alerts to designated contacts providing a GPS location of the device, the wrist-worn monitor was evaluated in 191 seizures of various types in an epilepsy monitoring unit. Fifty-one were generalized tonic-clonic seizures. The device detected 30 seizures (16% of the total), 16 (31%) of the generalized tonic-clonic seizures, and 16 (34%) seizures associated with rhythmic arm movements. Overall, only a minority of generalized tonic-clonic seizures or seizures with rhythmic movements were detected[48], discordant with previous studies. The reason for the discrepancy is unclear. Nevertheless, overall, the sensitivity for accelerometers to detect generalised convulsive and hypermotor seizures is considered to be excellent at between 90-95%, but tonic (sensitivity 67%[44]) and other motor seizures (18%[48]) are less reliably recognised. As expected, focal impaired awareness seizures without motor phenomena or absences are poorly detected with a sensitivity of only 2%.

Typically, seizures are detected 9-60 seconds after seizure onset which is an adequate window of opportunity for peri-ictal carer intervention and the false detection rate is generally low at <0.5 false activations per day which encourages continued use[45, 49-51]. Furthermore, the devices are typically unobtrusive and user-friendly[46].

3.2.2: Surface Electromyography

Epileptic seizures are typically associated with EMG activity in the 100-150Hz frequency band and this can differentiate epilepsy from non-epileptic movements. The preferred sites for placement of surface EMG recording electrodes are the deltoid, biceps and tibialis anterior muscles. In one small study of 11 patients and 22 seizures, the sensitivity for identifying generalised convulsive seizures was highest for the deltoid, at 100%, with only 57% sensitivity at the tibialis anterior. The false detection rates were excellent with only one false alarm every 10-12 nights of use. During wakefulness, the false detection rate was higher at one false alarm per day[52]. More recently, a larger study of 71 patients reported that the sensitivity of a wearable surface EMG device on the biceps muscle was 93.8% (30 out of 32 GTCS were detected) with a median seizure detection latency of 9 seconds (range -4 to 48 seconds) and false detection rate was 0.67 per day. There were no adverse events and none of the patients withdrew from the study [53]. A further study of a surface EMG device placed on the biceps, but utilising a different analysis algorithm, demonstrated an initial sensitivity of detecting convulsive seizures of 76%. With optimisation of the electrode placement over the midline of the biceps muscle this increased to 100% with a false alarm rate of 1.44 events per day. Adverse events were reported in 28%, and 9% of the patients withdrew from the study as a result[54]. Regarding tonic seizures, although the detection rate is lower at 53-63% this can be improved with personalisation of the algorithm parameters[55]. As expected, the detection of non-motor events is much less satisfactory[56], and adverse effects including risk of detachment, and discomfort and skin irritation from the sensor limit their usefulness outside of nocturnal convulsive or tonic seizures[57].

3.2.3: Pressure sensors

The recognition that most SUDEP related deaths occurred at night in bed led to the introduction of pressure sensors under bed mattresses. A sensor detects movement and pressure and activates an alarm if the parameters exceed a set threshold. The balance between the detection of normal and abnormal, seizure-related, movement is challenging and the false alarm rate for bed mattress pressure sensors can be prohibitively high leading to alarm fatigue and deactivation of the monitor. A number of systems have been developed and tested with variable success. Sensitivities range from unsatisfactory at 2.2% for the ST-2 system to detect any seizure, to an acceptable 78-85% for the Emfit monitor to detect nocturnal convulsive seizures with a satisfactory false alarm rate and activation time of 9 seconds after seizure onset[58-61]. The devices also have the advantage that they are unobtrusive, maintain privacy and are straightforward to use.

3.2.4: Visual tracking systems

Seizures associated with movement, but not just convulsive in nature, may be amenable to automated marker-based or marker-free video analysis techniques. These systems evaluate velocity, duration, oscillation, angular speed and motion trajectory to detect seizures[62, 63]. They are most effective for seizures associated with large movements, for example ictal head turning[64] or myoclonic jerks[63]. The sensitivity for these and other major seizures types is 75-100% with specificities of 53-93%[65, 66] and short seizure detection latencies of 10 seconds[66]. Furthermore, a recent study reported a correlation with the changing frequency of video-detected clonic movements towards the end of a convulsive seizure and PGES and this has specific relevance with respect to SUDEP risk[67, 68]. The marker-based systems may be hampered by sensor discomfort or displacement and all video analysis is dependent on positioning and exposure of the patient. The utility of video analysis systems in detecting more subtle motor activity, such as automatisms of focal impaired awareness seizures has yet to be determined.

3.3: Multi-modal devices

The value of monitoring biophysical parameters in the detection of seizures and potentially lowering the risk of SUDEP can be enhanced by acquiring multi-modal data through single or coordinated composite devices. In general, the use of multi-modal devices improves sensitivity and lowers the false detection rate[69].

Most combination devices utilise some form of movement detection such as an accelerometer in association with either electrodermal activity, heart rate, surface electromyography or video analysis.

The combination of an accelerometer with EDA improves the detection of motor episodes and seizures with autonomic disturbance. A number of devices have received medical clearance from the EU and FDA and are now commercially available[38]. Recent evaluation of the device demonstrated that with a sensitivity of detecting convulsive seizures at 94.5%, the false alarm rate is 1 event every 5 days. Importantly, with regard to SUDEP, no nocturnal seizures were missed. Furthermore, with a latency of 29.3 seconds, all detections occurred before the seizure ended. A rise in electrodermal conductance confirmed the presence of post-ictal autonomic dysfunction in 73% of the convulsive seizures. It was also noted that the multimodal wrist-worn device provided seizure counts that were more accurate than patient diaries, and this is important in ascertaining the impact of various interventions and determining the presence of ongoing convulsive seizure activity and accordingly SUDEP risk[70].

Accelerometers paired with surface EMG improve sensitivity in detecting convulsive and tonic seizures, achieving a 91% detection rate. Used individually the sensitivities were 82% for surface EMG and 86% for accelerometer data but in this study on paediatric patients, the false detection rate was higher, possibly due to increased baseline movements[71].

The combination of an accelerometer worn in an armband around the upper arm in addition to ECG monitoring via chest leads was evaluated in a multicentre study. Sensitivity for clinically urgent seizures of 87% was seen but at the expense of a high false alarm rate of 6.3 events per night. Furthermore, 45% of the patient data was lost due to technical difficulties with the wireless connection and internal sensor failures[72]. A more recent multicentre, prospective, home-based study evaluated the efficacy of a multi-modal device, with heart rate and accelerometer-based movement sensors, in patients with epilepsy and intellectual disability. Participants wore the device on the upper arm at night for 2 to 3 months. Twenty-eight of 34 admitted participants (1,826 nights, 809 major seizures) completed the study. The median sensitivity was 86% with a false-negative alarm rate was 0.03 per night. The false-positive alarm rate was highly variable with a range of between 0 and 6.3 false alarms per night. The multimodal sensor showed a better sensitivity than the Emfit bed sensor (median difference 58%) and the caregivers reported good adherence and usability[73].

The multi-modal intelligent seizure acquisition (MISA) system comprises a suit with 16 sensors, each one containing an accelerometer, gyroscope and gradiometer, in addition to 28 surface EMG electrodes on 14 muscles to comprehensively describe whole body movement[74]. The system has been tested on healthy subjects with simulated seizures and a single epileptic seizure with high sensitivity at 100% and low false detection rate[75]. The system is, however, cumbersome and complicated, and for some patients uncomfortable and this limits its applicability.

4: Summary

The use of devices in the management of health conditions, including epilepsy is expanding rapidly. At the very least, devices may improve the accuracy of seizure diaries by more objective measurements of activity and this may permit a more precise evaluation of the effectiveness of anti-epileptic treatment. Devices have the potential to provide reliable biomarkers for co-morbidities and possibly SUDEP, and also offer novel insights into the relationship between seizures and various environmental and internal factors.

Based on the available data, it can be proposed that the most appropriate seizure detection device for generalised tonic-clonic seizures, with sensitivities in excess of 90% and low false alarm rates, is either unimodal or multimodal surface EMG, EDA or accelerometers. For tonic seizures, surface EMG either in isolation or, in combination with, accelerometers affords sensitivities above 90%. Focal impaired awareness seizures are poorly detected with conventional movement-based devices and therefore either scalp or intracranial EEG, ECG / heart rate monitors or electrodermal conductance offer the best solution [see Table 1].

In this *Era of the Device,* the commercialisation of medical wearable technology should also be approached with some caution. Major technological, recreational and sporting companies are finding footholds in this $20 billion industry, and they bring with them substantial marketing and social media departments. Furthermore, a number of studies of devices are undertaken by the developing team or sponsored by the manufacturer and it is mandatory that robust scientific evidence continues to be the principal determinant of clinical decision-making. There are also significant issues with the acquisition, use and protection of personal information acquired from alert devices.

In this regard, the creation of standards for regulatory bodies to validate seizure detection devices has been proposed. This should include a number of evaluation phases commencing with simulated data, followed by a proof-of-principle study with, for example, up to 10 patients, and then larger and more robust studies with a reference standard and the acquisition of safety data, performed both in a monitoring unit and then in the home environment. The outcome measures that are deemed necessary to evaluate the performance of seizure detection devices include total recording time, device deficiency time, adverse effects, sensitivity, false alarm rate, detection latency and user experience scales. The creation of a large, open, database containing multi-modal annotated biophysical parameters from seizure and non-seizure periods from patients with epilepsy in order to test device algorithms would greatly facilitate the development of new devices and methods[76].

Future work is likely to focus on improving the sensitivity, false detection rates and usability of multi-modal devices and better integrating these with user-friendly GPS-enabled smart devices such as phones and watches. Furthermore, research investment is likely to specifically target SUDEP, once pathophysiological mechanisms have been further elucidated. It is very likely that non-EEG technologies to predict seizures with an acceptable degree of certainty will emerge and together these may impact on seizure-associated, and possibly SUDEP, risk and afford individuals with epilepsy greater independence. The vast quantities of physiological metadata acquired through these devices is ideal machine learning material and this may lead to a better understanding of the pathophysiological processes involved in seizure activity, ictal autonomic dysfunction and possibly SUDEP. Finally, additional closed-loop systems will be developed which monitor patient-specific parameters and respond to prevent or stop seizure activity via electrical stimulation or local drug delivery without additional user-intervention.

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Table 1: Summary of seizure detection devices

Device	Sensitivity	Seizure types	Advantages	Disadvantages
UNIMODAL				
Accelerometer	90-95% (GTCS, hypermotor)[44-47] 67% (tonic)[44] 2% (FIAS)	GTCS, hypermotor	Easy to use[46], relatively unobtrusive, widely available. Low false alarm rate of 1 event every 2-10 days	Motor seizures only. Free limb movement required.
Surface electromyography	94-100% (GTCS)[52-54] 53-100% (tonic)[55]	GTCS, tonic	Easy to use. Low false alarm rate of 1 event every 10-12 nights	Can be uncomfortable and become detached. Motor seizures only. Effectiveness is dependent on positioning
Piezoelectric bed sensor	Emfit 78-85% (GTCS)[58, 59, 61] 0-17% (FIAS)	Nocturnal GTCS	Easy to use, unobtrusive. Contact free. One false alarm every 2-19 nights[59]	Variable sensitivity, nocturnal seizures only, high false alarm rate during periods of wakefulness.
Electrodermal activity	100% (GTCS)[35] 86% (FIAS)[35]	All	Easy to use, relatively unobtrusive, EDA correlates with PGES, a biomarker of SUDEP. Suitable for use with FIAS.	Motion and pressure artefacts
Video-monitoring	75-100% (motor seizures)[65, 66] 75% (myoclonic)[63]	Motor seizures	Easy to use and relatively unobtrusive if marker-free system used. Frequency of clonic movements correlates with PGES	Reference markers can be uncomfortable or become displaced. Issues of privacy.
Cerebral blood flow	Saturation sensors 57.1% (pre-ictal GTCS)[41] NIRS 6-24% (pre-ictal various seizure types)[43]	All	All seizure types. Can detect pre-ictal changes.	Obtrusive, forehead sensors with additional occlusion required to reduce light pollution
EEG	Intracranial (by definition): Ictal 100%. Pre-ictal 66%)[7] Portable scalp (automatic seizure detection system): 73-96%[77]	All	Suitable for all seizure types, can provide pre-ictal warning	Scalp – obtrusive and uncomfortable, movement artefact Intracranial – risk of surgical complications

Cardiac – heart rate	36%-70% (pre-ictal)[14, 15] to 98% (ictal)[18] VNS (CBSDA) detection 66-74%[21, 22] Stimulation: 35-41%[21, 22]	All	Suitable for most seizure types, can provide pre-ictal warning. With VNS can also intervene	Most devices have obtrusive electrodes or require VNS implantation. VNS false activation rate can be high. Seizures without HR change are undetected.
Respiratory	SOMNO system 37.8% (simulated apnoea)[33] WADD 99.2% (simulated apnoea)[33]	All	Detects apnoea and may correlate best with SUDEP risk	Standard monitoring systems are obtrusive.
MULTIMODAL				
Accelerometer and EDA	94.5% (GTCS)[70]	GTCS	Easy to use, relatively unobtrusive, widely available. False alarm rate 1 every 2-5 days. Approved for medical use in EU & US	Motor seizures only. Free limb movement required. Daily recharging of commercially available device.
Accelerometer and sEMG	91% (GTCS and tonic)[71]	GTCS and tonic	Easy to use	
Accelerometer and HR	71%-87% (motor seizures)[72, 73]	Motor seizures	Easy to use, some systems are relatively unobtrusive.	Can be obtrusive if ECG leads used. Photoplethysmography is better tolerated. High false alarm rate.
Multimodal intelligent seizure acquisition (MISA)	98-100%[74, 75]	Motor seizures	Comprehensive evaluation of seizure related activity. Low false detection rate	Obtrusive – 16 sensors and 26 EMG electrodes

[GTCS: generalised tonic-clonic seizure; FIAS: focal impaired awareness seizure; PGES: post-ictal generalised EEG suppression; HR: heart rate, VNS: vagal nerve stimulator, CBDSA: cardiac based seizure detection algorithm; WADD: wearable apnoea detection device; sEMG: surface electromyography; EDA: electrodermal activity]