Seizure Detection Devices and Risk Assessment for SUDEP

MICHAEL R SPERLING, MD

JEFFERSON COMPREHENSIVE EPILEPSY CENTER

THOMAS JEFFERSON UNIVERSITY

PHILADELPHIA, PA, USA

Disclosures

- Research contracts: UCB Pharma, SK Life Science, Takeda, Neurelis, Cerevel, Engage Therapeutics, Eisai, Cavion, Xenon, Medtronic
- Consulting: Medtronic (fees to Thomas Jefferson University)
- Speaking (CME): Medscape, NeurologyLive, Projects in Knowledge, Eisai

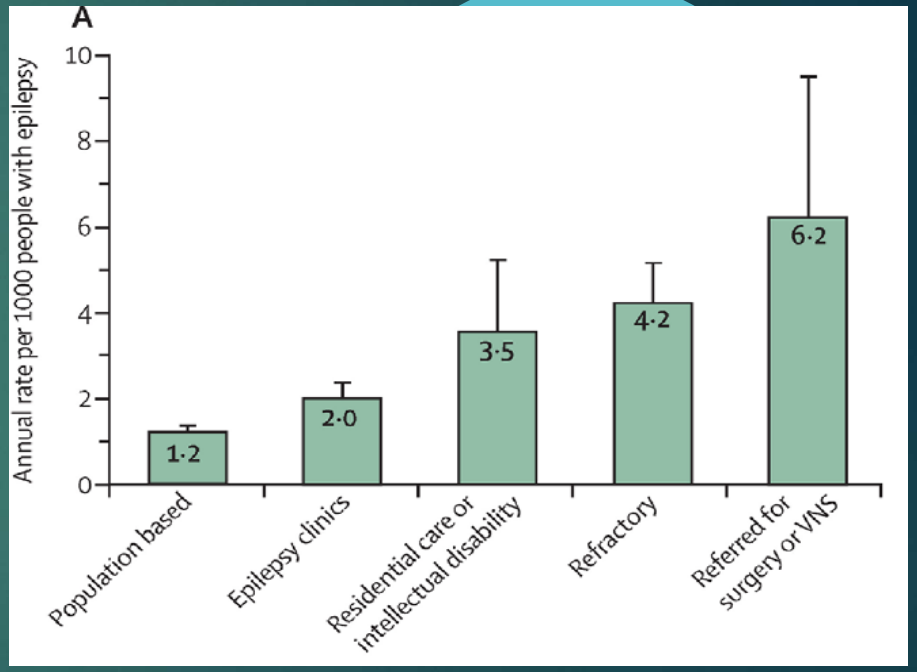
Criteria for SUDEP

- Sudden unexpected death of someone with epilepsy
- Death may be witnessed or unwitnessed
- With or without evidence of a preceding seizure
- Death is not secondary to documented status epilepticus, drowning, or trauma
- Autopsy does not reveal an anatomic or toxicological cause of death

- Definite SUDEP requires autopsy
- Probable SUDEP is applied when autopsy is not performed but the circumstances above are met
- Possible SUDEP is applied when autopsy is not performed and there is a potential competing cause of death

SUDEP

- Average incidence
  - 0.2 per 1000 person-years in children
  - 1.0 per 1000 person-years in adults with newly diagnosed epilepsy
  - 1-2 per 1000 person-years in people with chronic epilepsy
- In people with drug resistant epilepsy, incidence is 2.46-5.94 per 1000 person-years or higher
- Occurrence is probably underestimated due to attribution of deaths to other causes
- Pathophysiology is not understood – apnea often precedes asystole, usually associated with seizures, more often nocturnal, prone position



R Shankar et al. Epileptic Disorders 2017
C DeGiorgio et al. Front Neurol 2017
O Devinsky et al. Lancet Neurol 2016

ARS Question 1: SUDEP

- The risk of SUDEP is increased by what magnitude if someone has 3 tonic-clonic seizures per year rather than 2 tonic-clonic seizures per year
  A. Lower by 50%
  B. Same – no increase in risk
  C. Increased – 150%
  D. Increased 300%

Number of GTCS and SUDEP Risk:
Odds Ratios and 95% CI for GTCS and AEDs

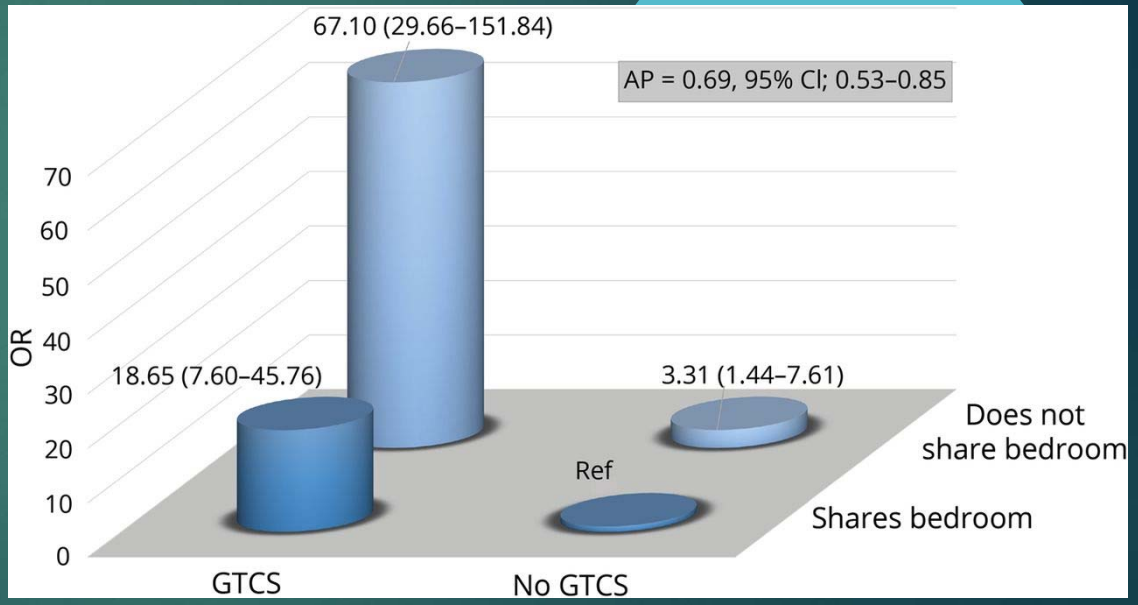
GTCS Seizure Frequency per Year	Adjusted Odds Ratio (GTCS and Number of Drugs
0	1.00 (ref)
1-2	6.4 (3.4-12.0)
≥3	15.5 (9.2-26.0)
Unknown	2.3 (1.2-4.5)

Key Point: Having few seizures leads to large increase in SUDEP risk

D Hesdorffer et al Epilepsia 53:249, 2012

Odds Ratio of SUDEP by Combinations of Generalized Tonic-Clonic Seizures and Living Conditions

- Nationwide case-control study in Sweden, deaths 2006-2011
- 255 cases (definite and probable), 1148 controls (with epilepsy, same gender, alive at time of death)
- People with SUDEP
  - Living alone: OR 5.01 (2.93-8.97)
  - GTCS: OR 9.60 (3.44-26.82)
  - GTCS in last year: OR 26.81 (14.86-48.38)
  - 1-3 GTCS: OR 22.14 (12.74-38.46)
  - 4-10 GTCS: ORA 31.87 (15.95-63.67)
  - No association with type of epilepsy (focal vs. generalized)



AP = attributable proportion due to interaction

O Sveinsson et al. Neurology e419-e429, 2020

Can We Do Something About This?

Modifying Mortality in Epilepsy:
Incidence of Death per 1000 Person-Years

	Placebo	AED at Effective Dose	AED at Ineffective Dose
Definite and probable SUDEP	6.9 (3.8-11.6)	0.9 (0.2-2.7)	3.7 (0.1-20.6)
Definite, probable, and possible SUDEP	6.9 (3.8-11.6)	0.9 (0.2-2.7)	11.1 (2.3-32.4)
Other cause of death	2.5 (0.8-5.8)	2.1 (0.9-4.4)	3.7 (0.1-20.6)
All causes of death	9.4 (5.7-14.7)	3.0 (1.5-5.6)	14.8 (4.0-37.9)

Odds ratio for SUDEP in treated group compared to placebo: 0.17 (0.05–0.57)
No difference for other causes of death

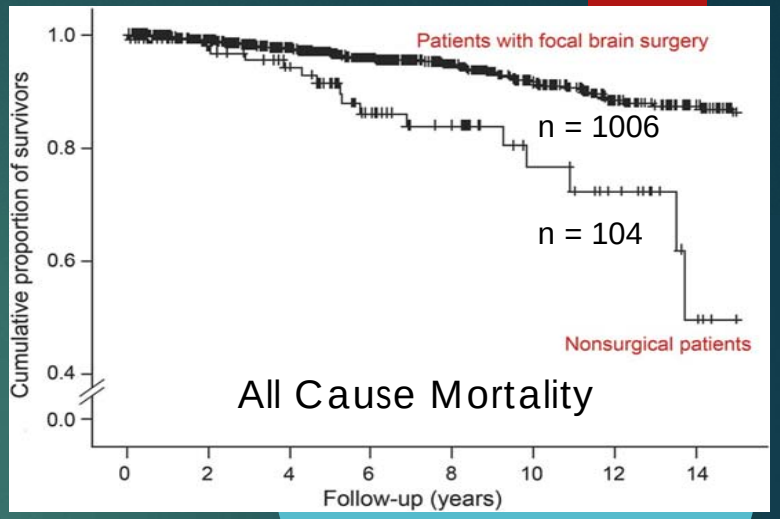
P Ryvlin et al. Lancet Neurol 2011

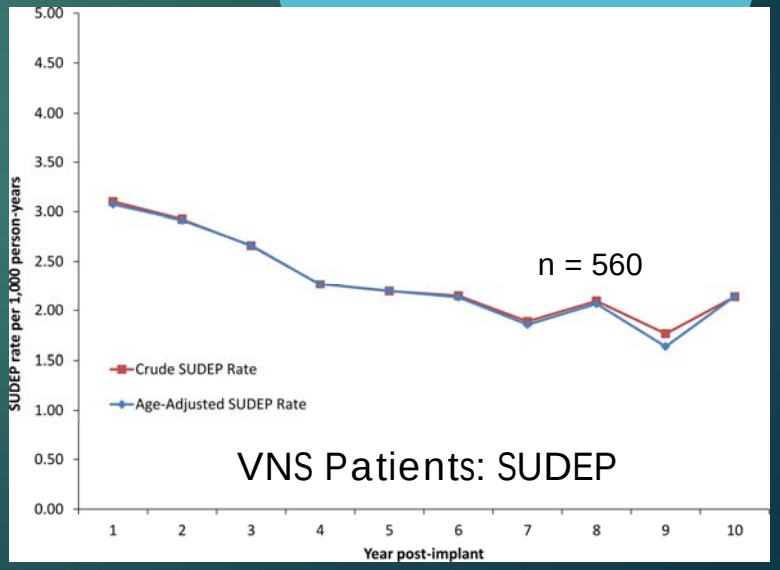
ARS Question 2: SUDEP

- Mortality risk in epilepsy can be modified by
  A. Resective surgery
  B. VNS
  C. RNS
  D. DBS
  E. All of the above

Modifying Mortality:
Brain Surgery and Stimulation

- Mortality rate is increased in intractable epilepsy
- After epilepsy surgery, there is a reduction in mortality with therapy
- VNS, DBS, and RNS are associated with reduced SUDEP risk
- Conclusion: treating seizures reduces risk of death and SUDEP





M Sperling et al. Neurology 2016
P Ryvlin et al. Epilepsia 2018

We Can Modify SUDEP Risk

- Stop seizures
  - Prescribe appropriate medical therapy at diagnosis
  - Aim for good adherence to medical therapy
  - Offer surgery when medications fail to control seizures
  - Keep offering medication if surgery fails
  - Offer neuromodulation (VNS, DBS, RNS) when surgery fails or cannot be done
- Make seizures milder
  - The bulk of risk comes from tonic-clonic seizures (but not all)
  - In focal epilepsy, if these can be converted to focal impaired aware or focal aware seizures, risk may be reduced
- Avoid living alone
- Avoid sleeping alone

Treatment Goal: Prevent Seizures

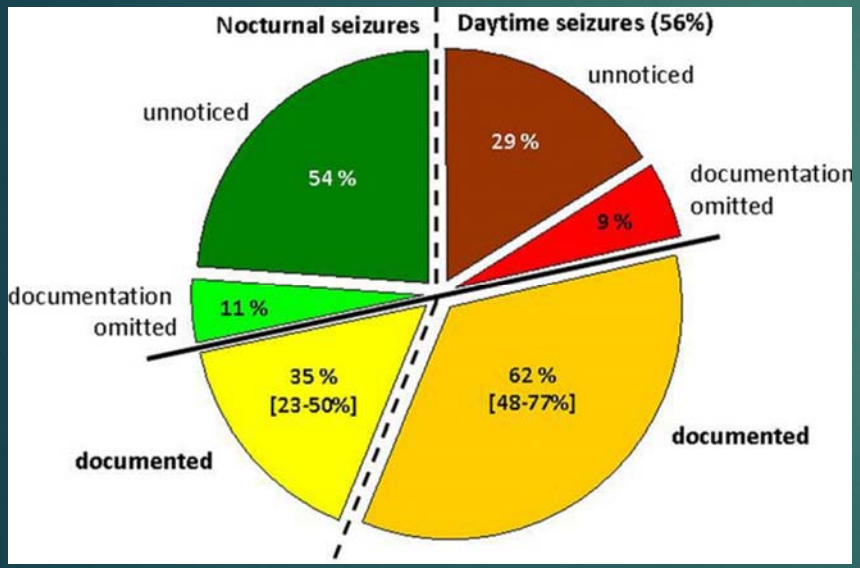
- To properly treat patients, we must accurately identify seizures
- KEY INDICATOR: SEIZURE
- SEIZURE DATA: HOW IS THIS DETERMINED? We rely upon the medical history to determine efficacy of therapy
- This requires reliable reporting of seizures
- Treatments are modified based upon patient and family reports
- We cannot prevent SUDEP unless we know we are preventing seizures

How Reliable is Our Data?

WHAT IS THE EVIDENCE?

Results of Patient Opinion Survey

Percentage of seizures noticed

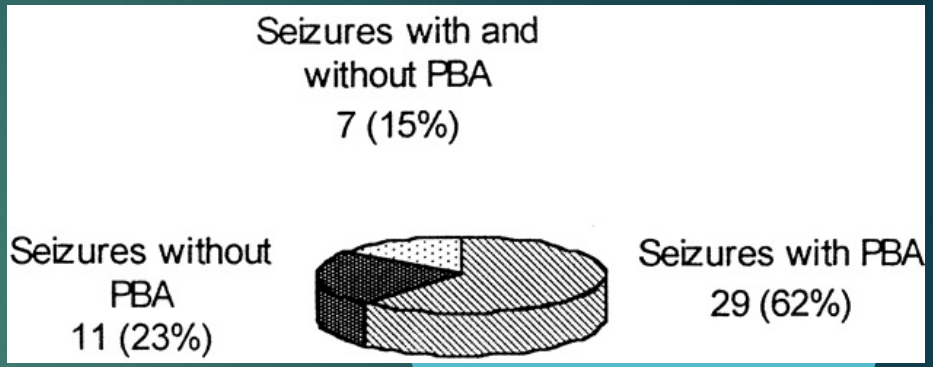


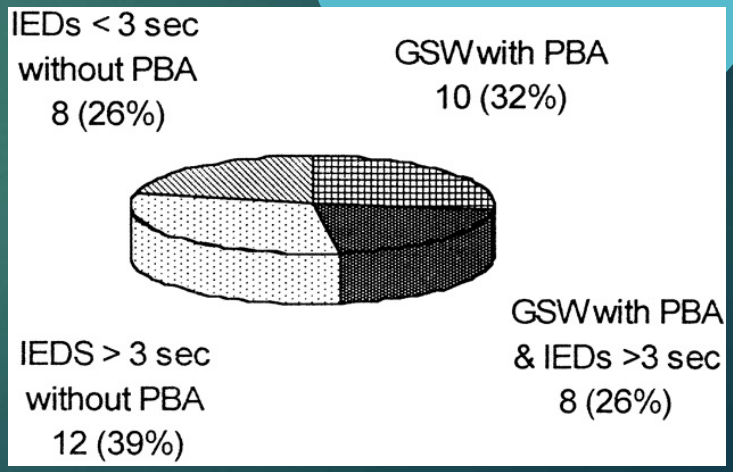
- Patients think they do not notice many of their seizures, especially at night
- 28% thought they never noticed daytime seizures, 47% missed more than half (n = 157 patients)
- 64% thought they never noticed nocturnal seizures, 79% missed more than half (n = 107)
- Family members noted more seizures, but still thought they missed many seizures
- CONCLUSION: PATIENTS THINK THEY ARE NOT RELIABLE AT REPORTING SEIZURES

B Blachut et al Seizure 2015

Ambulatory EEG Seizure Detection

- 552 ambulatory EEG from 502 patients, 16 channel
- No EEG change for 854 patient alarms (headache, dizziness, confusion, eye flutter, stare, chest pain, psychological symptoms, palpitations)
- A seizure was noted on EEG for 132 patient alarms (13.4%)
- 47/552 records had focal seizures but only 29 (61.7%) were identified by patients; in 11/47 EEGs, seizures were detected solely by computer
- Generalized spike-wave bursts were often unrecognized





W Tatum et al J Clin Neurophys 2001

Why Is This a Problem?

- Our primary criteria for assessing treatment efficacy relies on FLAWED data
  - Patients and families often do not notice seizures
  - Patients and families often report symptoms that may not be seizures
  - This is particularly true for nocturnal seizures (which pose greater SUDEP risk) and non-convulsive seizures which may be subtle and go unnoticed
- Our treatment decisions rely on unreliable data – unsupported belief that treatment is effective
  - Assessing that a patient is controlled when this is false puts patients at risk
  - Assessing that a patient is uncontrolled when this is false puts patients at risk – unnecessary alterations of therapy, restrictions
- Medical and lifestyle decisions that affect safety rely on flawed data
- What are the consequences? Increased SUDEP risk

Detection Methods: Single and Multiple Modality Detection

- Dogs
- EKG
- EMG
- Accelerometry
- Pressure
- Electrodermal activity
- Video
- Temperature
- Photoplethysmography
- EEG

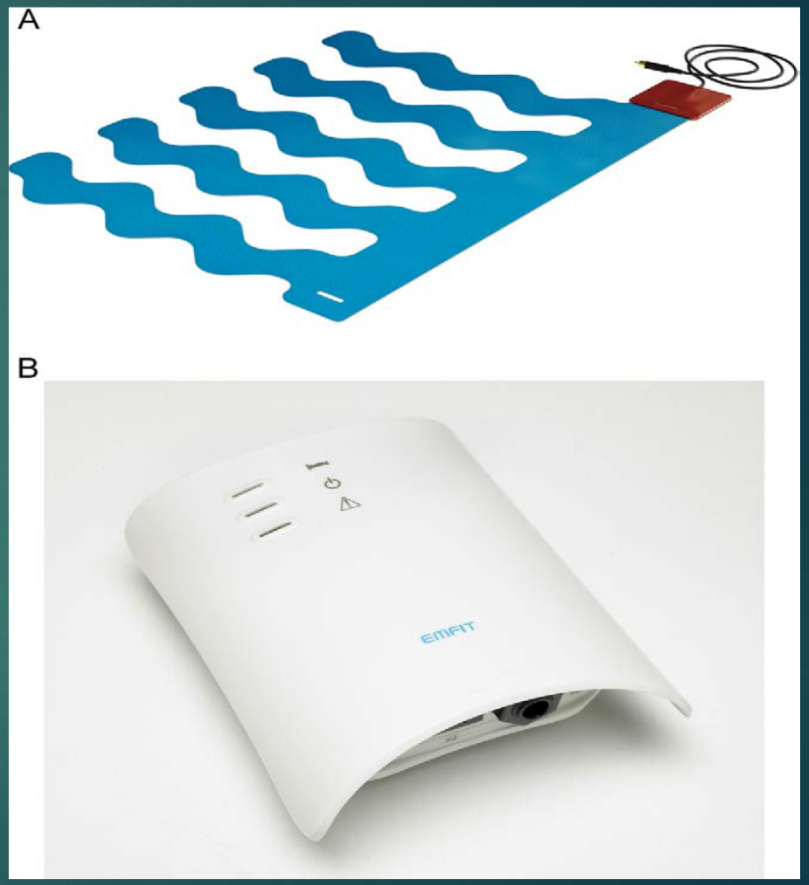
Seizure Detection

- Sensitivity and specificity are critical
- Require accurate detection of seizures
  - At present, work has focused on tonic-clonic seizures – characteristic movement patterns, EMG pattern, changes in heart rate, EDA, observable behavior – focus because of concern for SUDEP, injury
  - Poor detection of other seizure types
- Must have low false positive rates
  - Excessive false detections makes the device much less useful, and patients will not wear it (devices behave differently in different people)
  - Much testing is done in epilepsy monitoring units, where movement is limited – much device testing not “real world”

Movement Detection

Bed Alarm (Emfit)

- 45 patients monitored
- 26 had 78 seizures
- Detected 11/13 (84.6%) of tonic-clonic seizures while asleep, and 12/16 (75%) awake; detected 5/14 FIA with motor involvement
- Generally much lower detection rates for other seizure types
- Suitable for tonic-clonic seizures in sleep
- Requires no daily effort/compliance by patient
- Time of highest risk for SUDEP

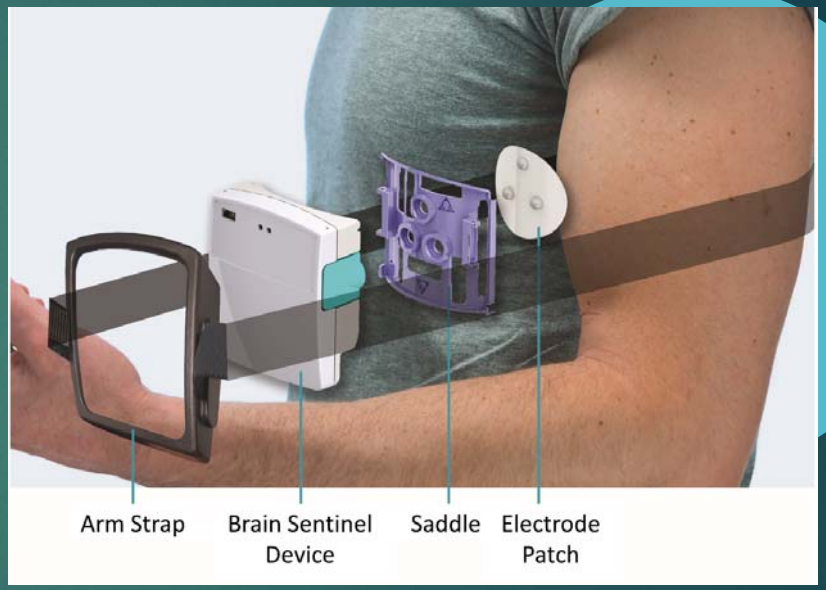


Van Poppel et al. J Child Neurol 28:1434, 2013

EMG Detector

EMG Detectors: Objective is Detection of Tonic-Clonic Seizures

NIghtwatch

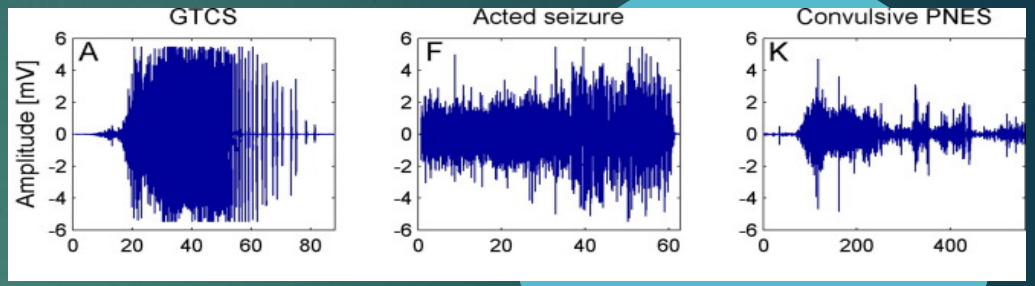


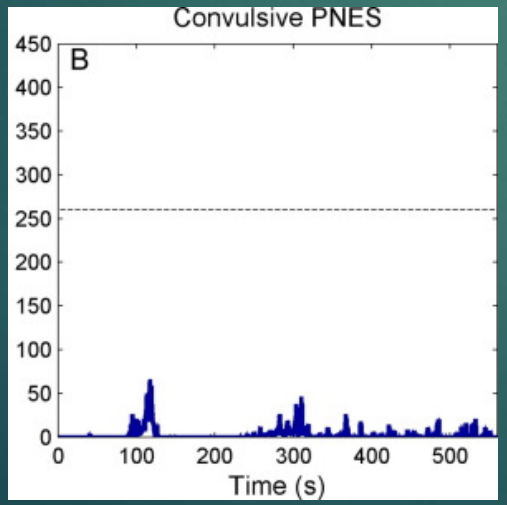
SPEAC by Brain Sentinel

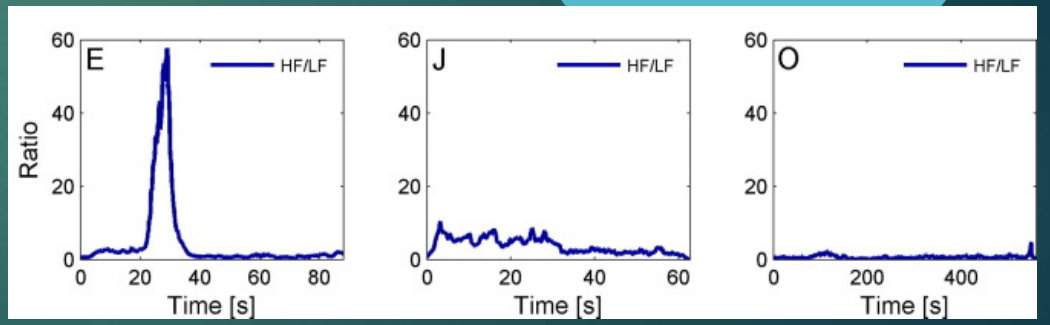
Halford J et al. Epilepsia 58:1861, 2017

EMG Processing of Seizures

- A, F and K shows the EMG signals. B shows the evolution of the median frequency throughout the three conditions.
- E, J and O show the evolution of the HF/LF ratio.







Beniczky S. Clin Neurophys 127:2900, 2016

Seizure Detection with EMG

- Beniczky study: device sensitivity was 93.8%, detecting 30 of 32 GTCS (95% CI 86%–100%), mean latency to detection: 9 seconds
  - Both missed seizures were the second seizure after a detected first seizure
  - False positive rate of 0.67 seizures/day, 47/71 patients (66%) had no false positive detections (exercise accounted for 68% of FA)
  - 161 other seizures occurred (including 14 PNES) – none detected
- Halford study: device sensitivity was 76%, detecting 35 of 46 GTCS
  - With optimal placement, 29 of 29 GTCS detected
  - False alarm rate of 2.5/day (nearly half of patients had no FA)
  - 9% withdrew because of device irritation

Halford J et al. Epilepsia 58:1861, 2017; Beniczky et al. Neurology 90:e428, 2018

Wristband – Wearable Devices

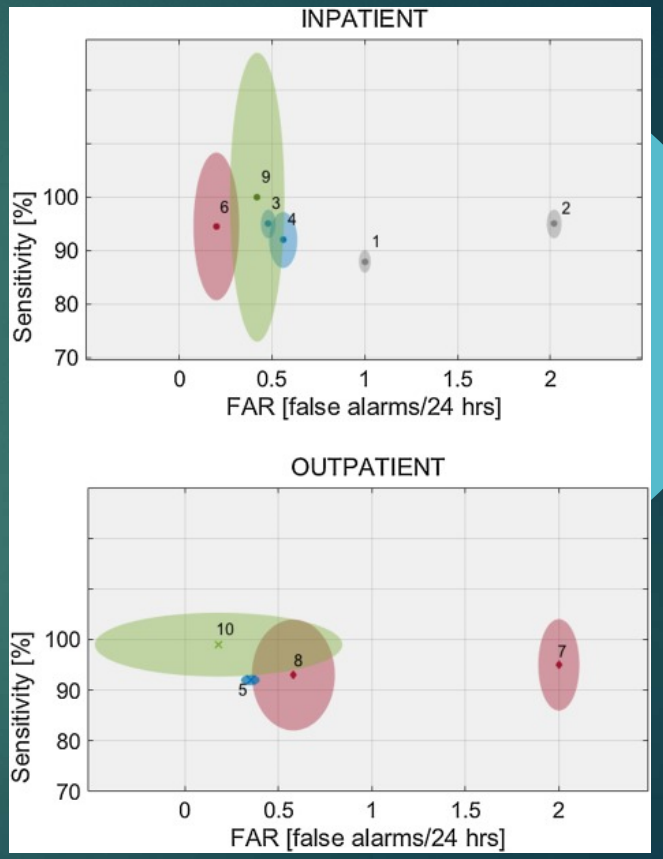
Multimodal Wrist Band Detection

- Empatica Embrace 2: accelerometer, EDA, temperature, gyroscope (FDA approved)
- E4: accelerometer, EDA, photoplethysmography, temperature sensors (research)
- SmartMonitor Smartwatch Inspyre: uses accelerometer on Samsung or Apple watches and will send an alarm (connected to cell phone) (it is an app)
- Geared to detecting seizures with convulsive activity

Regalia G et al. Epilepsy Res 2019

False Alarm Rates (FAR) for Wrist Band Detectors

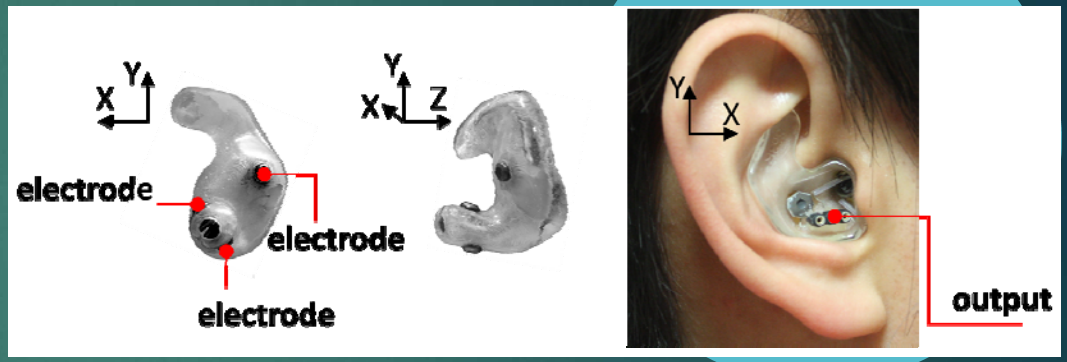
- Combined accelerometer and EDA with Embrace: 94.6% sensitivity and FP 0.2/day, mean latency 29.3 sec (range15-151 sec) for T-C seizures
- Algorithm evolution of false alarm rate (FAR), beginning at 1-2 per day, reducing to 0.5 or less per day over 10 studies
- Note that #7 and #8 are outpatient trials, with FAR of 1-2/day
- Challenge is to minimize FAR, or device will not be worn in patients with infrequent seizures



Regalia G et al. Epilepsy Res 2019; Gutierrez E et al. Epilepsia 59 (supp1) 36, 2018

EEG Detection

Imec EEG system

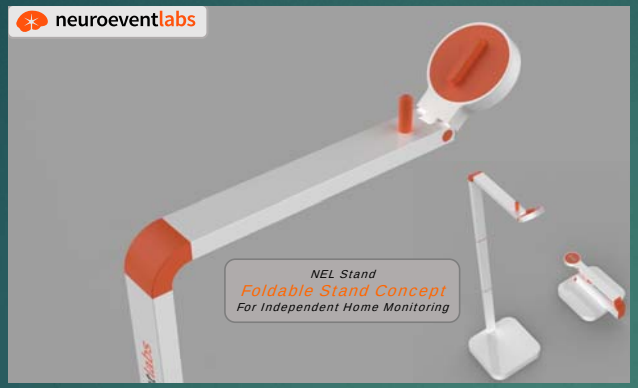


Ear EEG, collaboration of Imperial College London and University of Aarhus; discreet

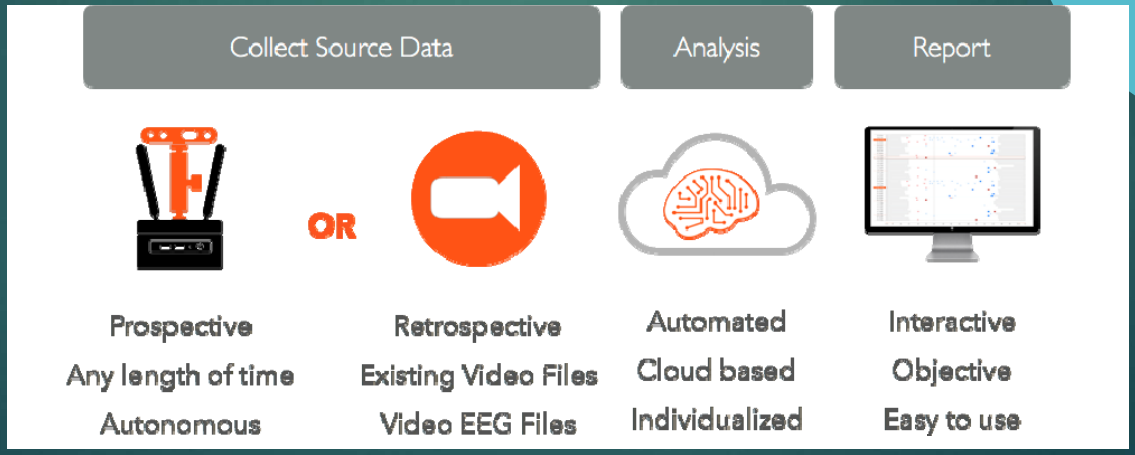
Practical limitations for daily function, must be combined with other modalities because of artifact

Video Detection Using Artificial Intelligence

Machine Learning Based Seizure Detection and Classification detection and classification



Nelli Home	Nelli Ward
Easy to install	Fixed or mobile installation
Fully automated, records when patient present	Manually start and stop monitoring
Analysis delivered within 2 weeks	Analysis delivered within 2 working days
Intended for longer monitoring periods	Intended for short monitoring periods
Diagnosis, intervention,	Pre-screening, complex case diagnostics



Feature Extraction

Looks for seizure phenomena across seizure types by focusing on visible and audible movement structures (behaviors).

SHALLOW

DEEP

Audio level

Essential motion

Oscillation

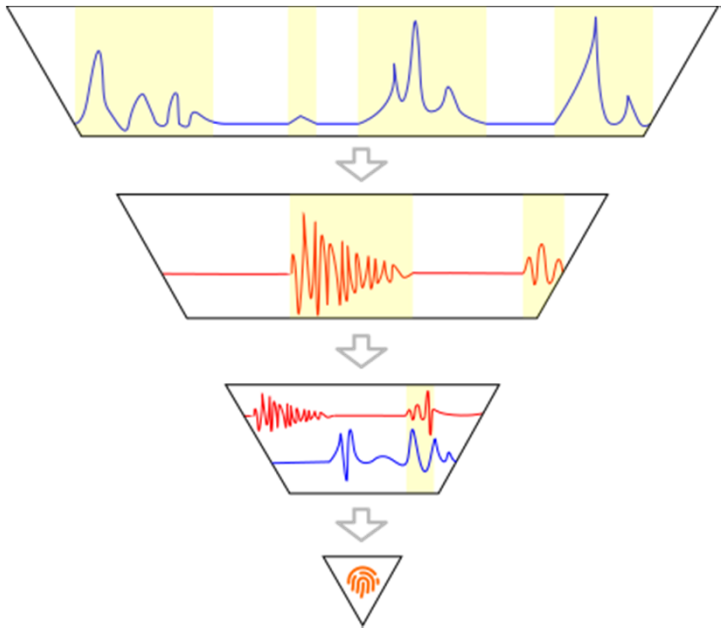
Respiration rate

Sound profile

Hand orientation

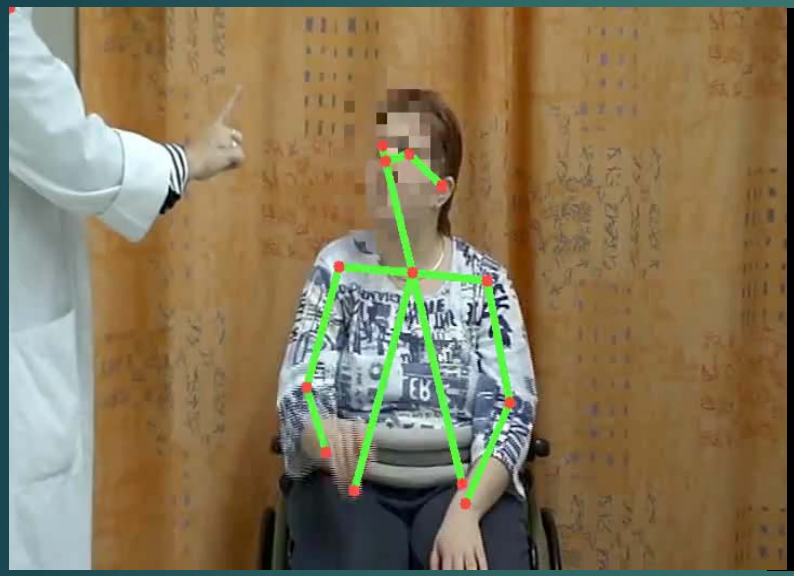
Facial analysis

Pose estimation



Feature Extraction in Action

Pose estimation



Respiratory rate

ARS Question 3: Seizure Detection

- Barriers to routine use of seizure detection include
  A. High false alarm rates
  B. Low false alarm rates
  C. Ease of detection of all seizure types
  D. Fragility of equipment

Needs in Seizure Detection

- Methods to facilitate patient adherence
- Reliable detection of seizures other than tonic-clonic seizures
  - These too are associated with injury and death
- Significant advances are required, new concepts
- Extremely low false positive rate – required for most interventions
  - Alerting other individuals (false positive alarms cannot outnumber true detections, problem for people with infrequent seizures)
- With reliable detections, interventions can be employed

The Role of Ambulatory Seizure Detection

- Compensate for inadequate reporting of seizures by patients and families/caregivers
- Offers ability to prescribe therapy based upon objective, verified data
- Potential for improved seizure control – discover who is still having seizures but is unaware of it
  - Alter therapy to suit situation
- Potential for fewer drug side effects in some
  - Avoid over-treating symptoms that are not seizures
  - Earlier diagnosis of non-epileptic symptoms

Conclusion

- We live in an exciting time
- Existing and new technologies can be employed for diagnostic and therapeutic purposes for people with epilepsy
- The only limiting factors are our imagination and willingness to try something new
- Benefits include improved therapy leading to greater safety, reduced mortality and lower morbidity

Wright brothers
59 sec flight (1903)

Singapore to New York

Airbus 350-900ULR: 19 hours, 9000 nautical miles