PRINCE OF SONGKLA UNIVERSITY

Explore • Commit • Discover

EPILEPSY HIGHTLIGH 2020

Professor Kanitpong Phabphal

Prince of Songkhla University

AIMS

- Update and highlight
- Without going into much detail
- Thai patients with epilepsy: co-morbidity
- Suggestions for further reading

OUTLINE

- New era in EEG monitoring
- New era of personalized epilepsy management
  - Gene therapy
  - Automated seizure detection using wearable devices
- Co-morbidity: OSA
- Epilepsy Network
- Suggestion for further reading

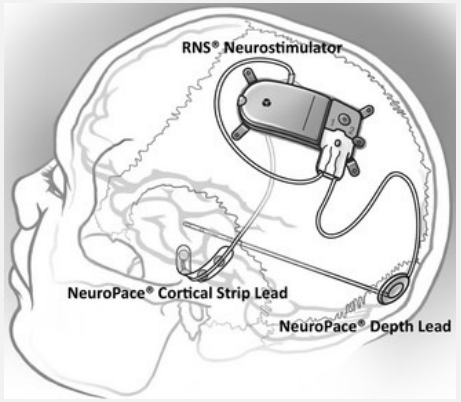
A NEW ERE IN EEG

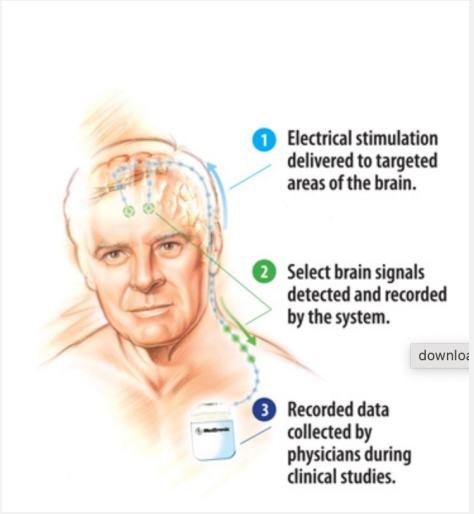
- The average accuracy of seizure diaries is <50%
- Scalp EEG has several critical limitations for long-term monitoring
- Scalp electrodes are generally acceptable for periods of up to 1-2 weeks at most
- Subscalp EEG: remove electrode care, avoids skin abrasions, and secures a stable and low-impedance recording

- Two commercially available intracranial devices enable chronic EEG monitoring
  - NeuroPace
  - Percept PC (Medtronic)
- The novel class of subscalp EEG recording devices

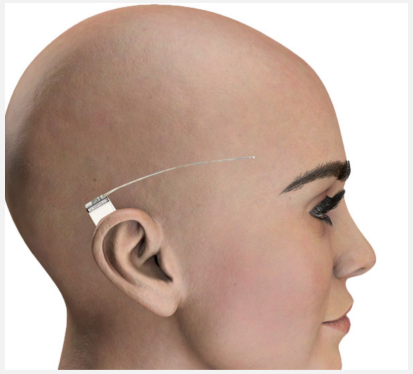
INVASIVE EEG DEVICES

Intracranial

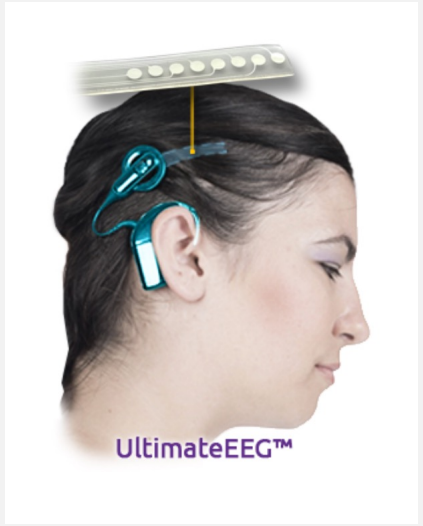




Subscalp

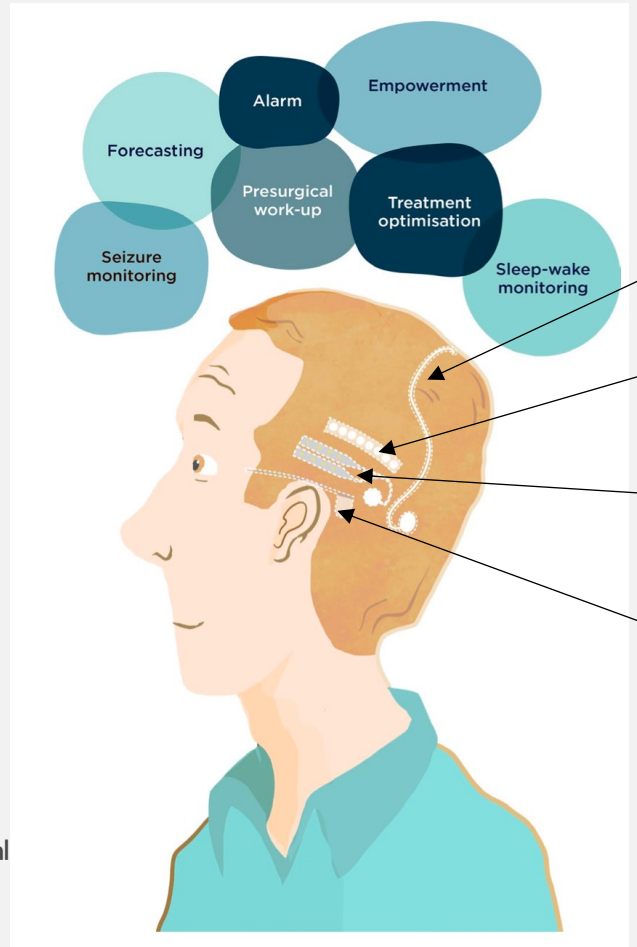


24/7 EEG SubQ from UNEEG medical



UltimateEEG from BrainCare Oy, Finland

A NEW ERE IN EEG



Minder from Epi-Minder

UltimateEEG from BrainCare Oy

the Epios system from the Wyss Center for Bio and Neuroengineering

24/7 EEG SubQ from UNEEG medical

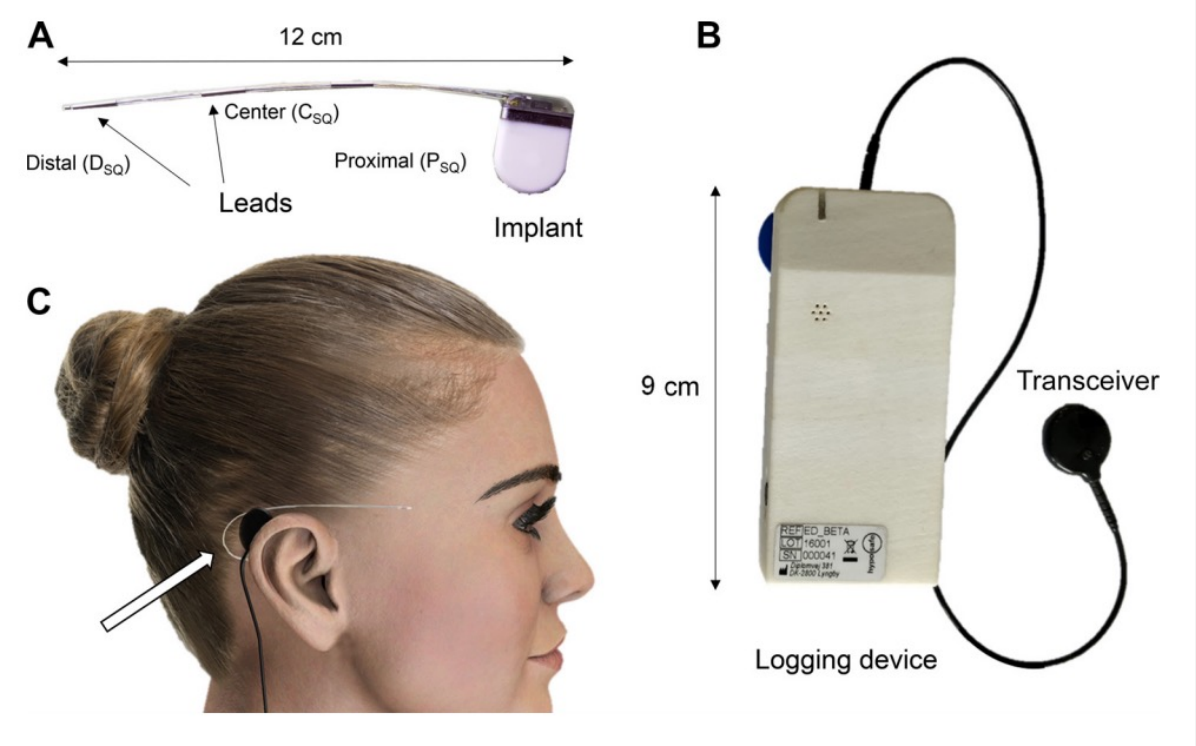
SUBSCALP EEG

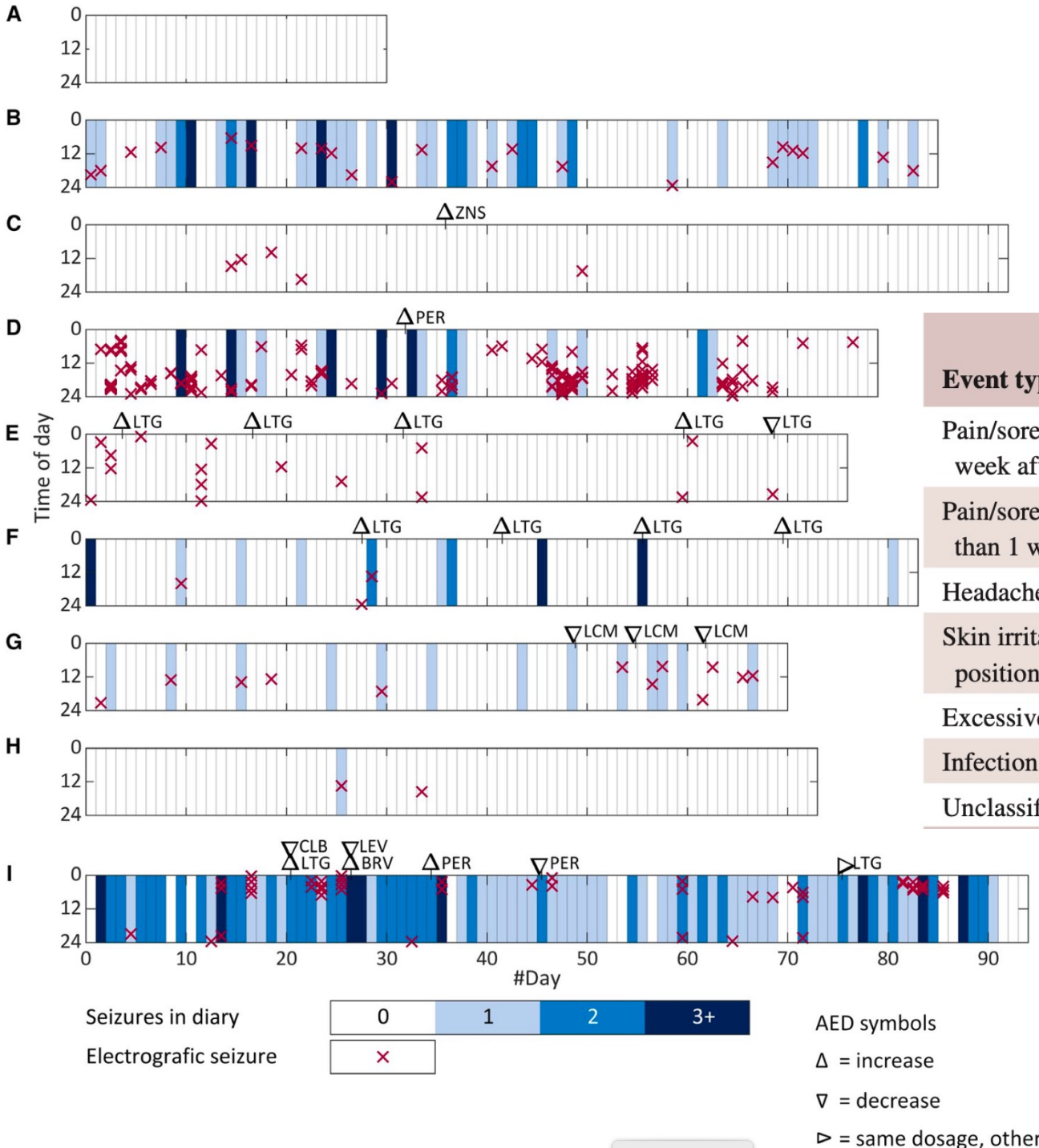
- Ultra-long term (ie, > 1 month and potentially for many months or years)
- Home environment, temporal fluctuations in pattern of seizure (personalized epilepsy management)
- Alternating seizure localization in some individuals with multifocal epilepsies

ULTRA-LONG-TERM SUBCUTANEOUS HOME MONITORING OF EPILEPSY – 490 DAYS OF EEG FROME NINE PATIENTS

Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW, Kjaer TW. Epilepsia2-19;602204-14

27-64 years
Medical refractory epilepsy
≥ I seizure/month

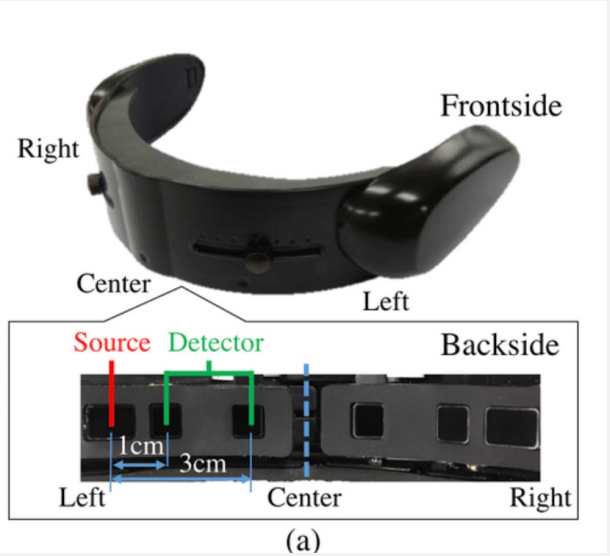




Event type	No. of occurrences	Severity	Anticipated
Pain/soreness at site of surgery up to 1 week after surgery	6	Mild	Yes
Pain/soreness at site of surgery more than 1 week after surgery	2	Mild	Yes
Headache not related to surgery	2	Mild	Yes
Skin irritation at transceiver contact position	2	Mild	Yes
Excessive bleeding	0	—	—
Infection	0	—	—
Unclassified	1	Mild	No

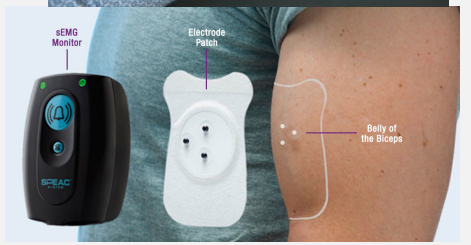
Device	Channels/montage	Recording modalities	EEG sampling rate	Battery	Wearable companion	Continuous raw data available	Status
CE-approved devices							
24/7 EEG SubQ	2 channels/unilateral	EEG + 3 axis accelerometry	207 Hz	External/24 h rechargeable	Yes	Yes	CE-marked by April 2019
Devices in validation phase							
Minder	2 channels/bilateral	EEG	[a]	External/24 h rechargeable	Yes	Yes	Clinical trial is ongoing
EASEE	4 channel/unilateral Laplacian	EEG	[a]	[a]	Yes	[a]	Clinical trial is ongoing
Epios	7 channels/temporal OR 14 channels/ bitemporal OR 28 channels/full montage	EEG + ECG + audio + 3 axis accelerometer	250 Hz	External/24 h rechargeable	Yes	Yes	Clinical trial to start in 2020
Neuroview Technology	1 or 2 channels/ unilateral	EEG + 3 axis accelerometry	256	Internal/1 y	No	No; only relevant epochs	Clinical trial to start in 2020
UltimateEEG	Up to 8 channels/ unilateral	[a]	[a]	[a]	[a]	[a]	Clinical trial to start in 2020

AUTOMATED SEIZURE DETECTION USING WEARABLE DEVICES



- Wrist 3D-accelerometer
- Wristwatch accelerometer (SmartWatch)
- Surface EMG
- Cardiac-based seizure detection algorithm (Aspire)
- Heart rate (ECG)
- Heart rate (ECG and photoplethysmography (PPG))
- Video-based algorithm in a residential care setting.
- Under-mattress device (ElectroMechanical Film Emfit!)
- Behind-the-Ear-EEG
- Closed-loop implantable neural stimulators

- Heart rate (photoplethysmography) and 3D-accelerometer
- Heart rate (ECG), arterial oxygenation, electrodermal activity
- Heart rate (ECG) and accelerometer
- Wristband electrodermal activity (EDA) and accelerometer
- Near infrared Spectroscopy (NIRS)



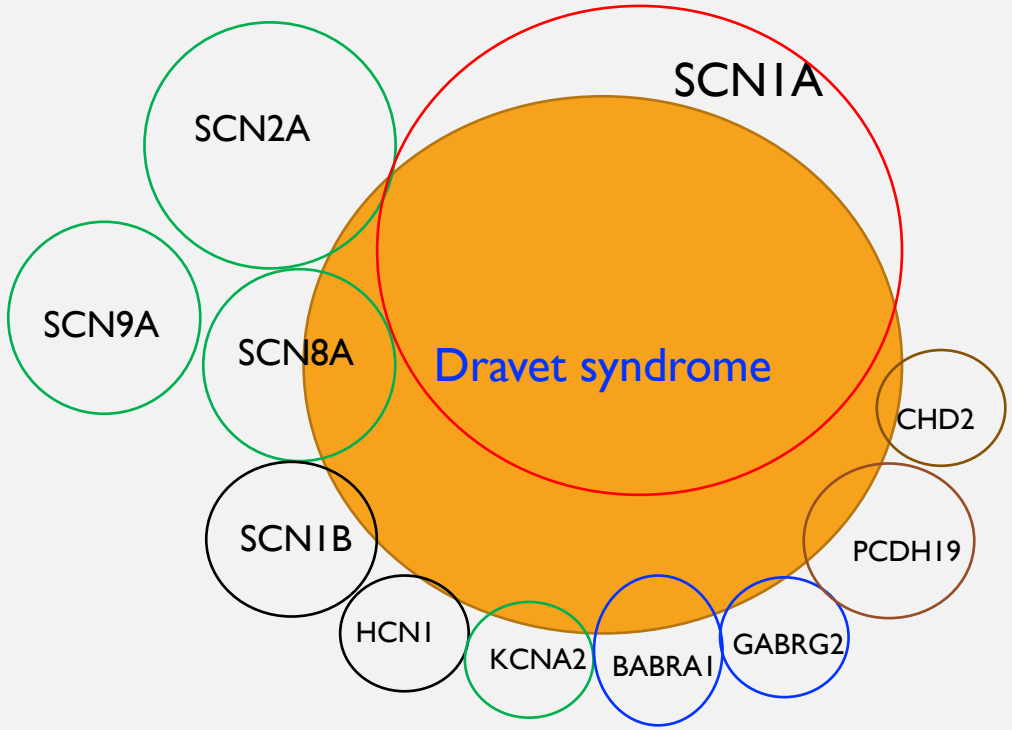
CURRENT RECOMMENDATIONS-ILAE 2021

Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology

- Wearable devices are effective for accurate detection of generalized tonic-clonic seizure and focal-to bilateral tonic-clonic seizure
- It is uncertained whether the detection alarms result in meaningful clinical outcoms for patients until further research is completed
- Wearable devices are recommended for detection of tonic-clonic seizure (weak/conditional recommendation).

Beniczky et al. Clinical Neurophysiology 132 (2021) 1173–1184

TREATMENT OF GENETIC EPILEPSY



JAMA Neurology | Original Investigation

Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens
A Randomized Clinical Trial

JAMA Neurol. 2020;77(3):300-308.

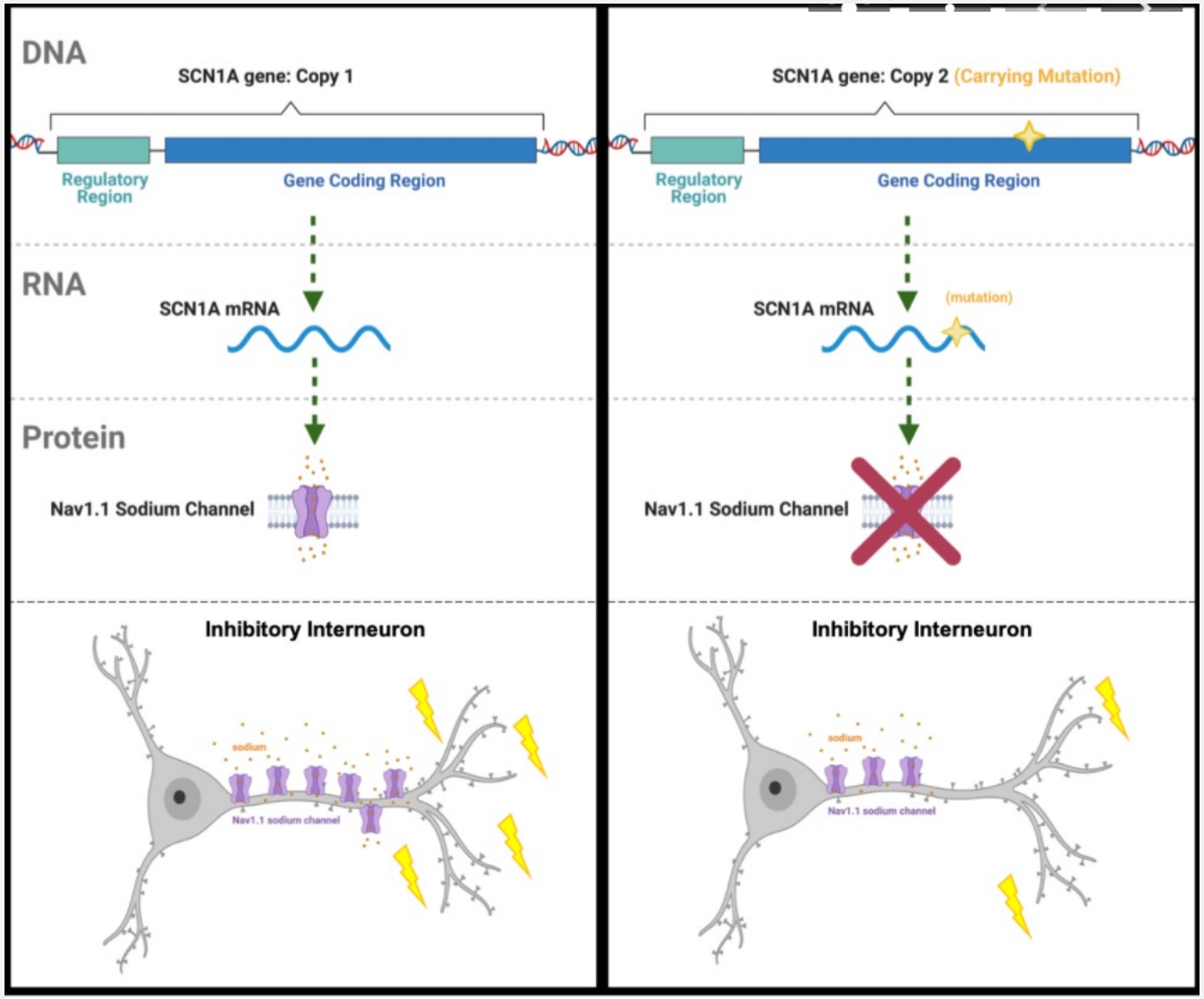
Rima Nabbout, MD, PhD; Arun Mistry, MBChB, MRCP(UK), MRCPCH; Sameer Zuberi, MD; Nathalie Villeneuve, MD; Antonio Gil-Nagel, MD; Rocio Sanchez-Carpintero, MD; Ulrich Stephani, MD; Linda Laux, MD; Elaine Wirrell, MD; Kelly Knupp, MD; Catherine Chiron, MD, PhD; Gail Farfel, PhD Bradley S. Galer, MD; Glenn Morrison, PhD; Michael Lock, PhD; Anupam Agarwal, MD; Stéphane Auvin, MD, PhD; for the FAiRE, DS Study Group

Fenfluramine + stiripentol

- > 25% seizure reduction: 70% seizure reduction in fenfluramine vs 27% in placebo
- > 50 % seizure reduction: 54% seizure reduction in fenfluramine vs 5% in placebo
- > 75% seizure reduction: 35% seizure reduction in fenfluramine vs 2% in placebo
- Significantly longer seizure-free interval (22.0 vs 13.0)

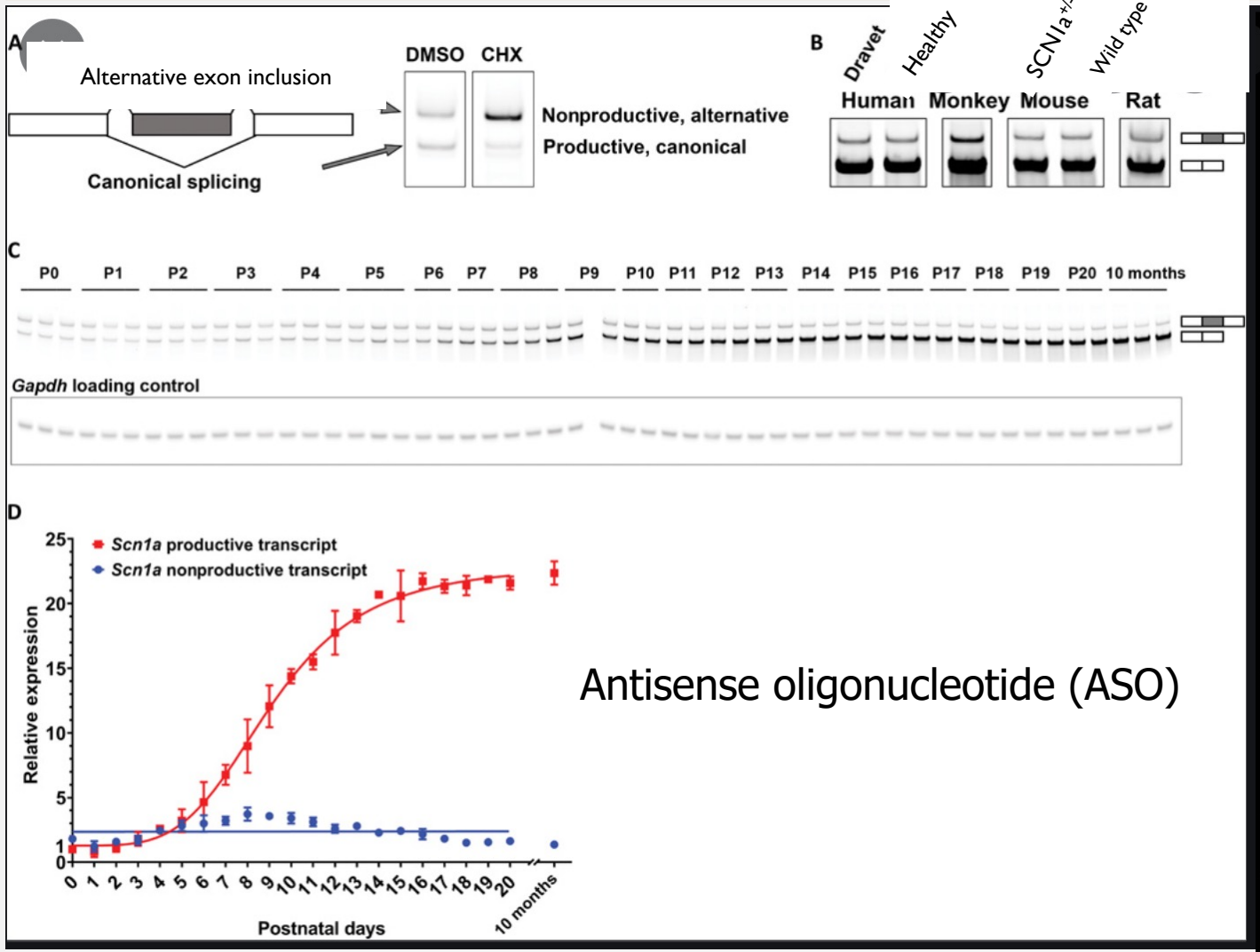
Table 3. Most Common (≥10%) Noncardiovascular Treatment-Emergent Adverse Events in Any Treatment Group

Outcome	Patients, No. (%)	
	Receiving Fenfluramine (n = 43)	Receiving Placebo (n = 44)
Patients with ≥1 treatment-emergent adverse event.	42 (98)	42 (96)
Patients with ≥1 serious treatment-emergent adverse event.	6 (14)	7 (16)
Treatment-emergent adverse events in ≥10% of patients in any treatment group		
Decreased appetite	19 (44)	5 (11)
Pyrexia	11 (26)	4 (9)
Fatigue	11 (26)	2 (5)
Diarrhea	10 (23)	3 (7)
Nasopharyngitis	7 (16)	15 (34)
Blood glucose decreased	6 (14)	2 (5)
Lethargy	6 (14)	2 (5)
Bronchitis	5 (12)	2 (5)
Seizure	2 (5)	7 (16)

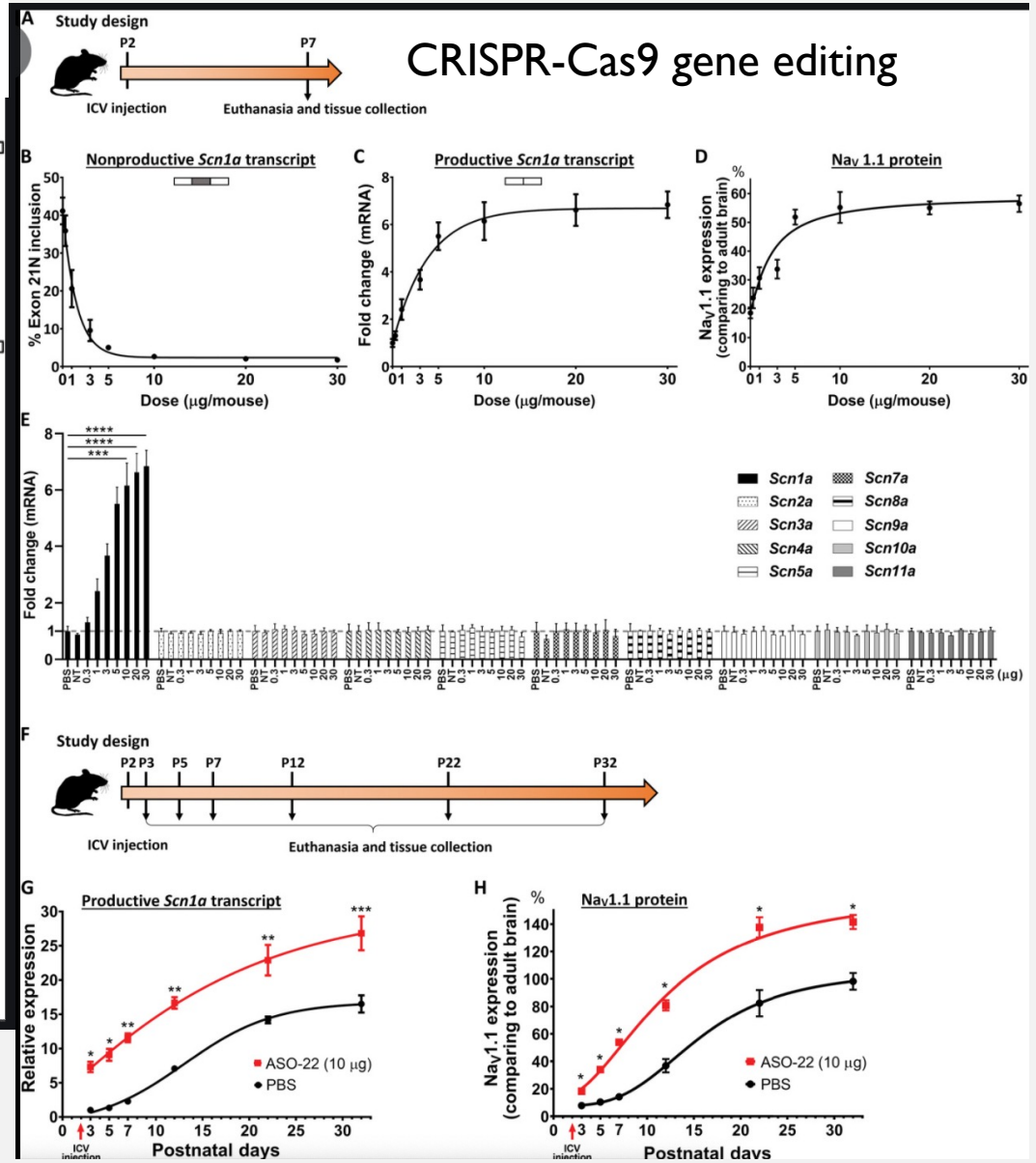


https://www.dravetfoundation.org/gene-therapy-for-dravet-syndrome/การเกิด

Potential gene therapy



Antisense oligonucleotide (ASO)



Epilepsynhighlingt 2020

Lagae et al. Lancet 2019; 394: 2243-54.

Nabbout et al. JAMA Neurol 2020; 77: 300-8.

CO-MORBIDITY IN EPYLEPSY

SLEEP BREATHING IN EPILEPSY

- Sleep-disordered breathing: a group of disorders characterized by intermittent pauses in breathing, which may disrupt the normal architecture of sleep and cause increased sympathetic activation, hypoxia, hypercapnia, and shifts to cerebral blood flow
- These include obstructive sleep apnea disorders, central sleep apnea syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder
- Bidirectional
  - The effect of sleep on spilepsy: epileptic syndrome, idiopathic epilepsy, symptomatic epilepy, symptomatic (Focal and Generalized)
  - The effects of epilepsy on sleep (subjective sleep quality, sleep architecture, sleep apnea)
  - Nocturnal epilepsy vs parasomnia

SLEEP-DISORDERED BREATHIN AND EPILEPSY

- Sleep-disordered breathing is also associated with significant quality of life, cardiovascular-related disease and mortality including ischemic disease and sudden death.
- Epilepsy have increased cardiovascular-related mortality and morbidity including hyper- tension, heart disease, and stroke.

OSA AND EPILEPSY

- OSA is a highly prevalent disorder, affecting 24% of men and 9% of women. Young et al. N Engl J Med 1993.
- OSA was confirmed by ambulatory PSG in 73% of 40 patients identified as OSA suspects using a structured interview. Manni et al. Epilepsia 2003.
- PSG study that involved patients with drug-resistant epilepsy unselected for sleep disorder symptoms 33% of 39 adults had OSA. Malow et al. Neurology 2000.
- PSG study in ambulatory epilepsy clinic, OSA prevalence was 30%, 16% having moderate-severe disease, rates that markedly exceed general population estimates. Foldvary-Schaefer et al. Epilepsy behave 2012.
- Understanding the predictors of OSA in epilepsy is important since treatment of OSA has been shown to reduce seizures in 40-86% of patients including adults and children. Devinsky et al. Neurology 1994, Hollinger et al. Malow et al. Malow et al. Eur Neurol 2006, Vaughn et al. Neurology 1997 Neurology 2008, Vendrame et al. Seizure 2006, epilepsia 2011.

DIAGNOSIS OF OSA IN EPILEPSY

- PSG
- Screening tools
  - STOP-BANG
  - Sleep Apnea scale of the Sleep Disorder Questionaire (SA-SDQ)
  - STOP-BAG
  - Neck, Obesity, Snoring, Age, Sex (NoSAS) Score

Screening tools	AUC			
	AHI ≥ 5 (95% CI)	AHI ≥ 10 (95% CI)	AHI ≥ 15 (95% CI)	AHI ≥ 30 (95% CI)
STOP-BANG	0.69 (0.60-0.77)	0.67 (0.5-0.76)	0.62 (0.50-0.74)	0.64 (0.49-0.79)
STOP-BAG	0.69 (0.60-0.78)	0.65 (0.56-0.75)	0.62 (0.51-0.74)	0.61 (0.45-0.76)
SA-SDQ **Total** **Male** **Female**	0.76 (0.68-0.83) 0.68 0.73	0.67 (0.58-077) 0.67 0.64	0.67 (0.55-0.78) 0.66 0.64	0.68 (0.51-0.85) 0.63 0.72
NoSAS	0.78 (0.71-0.86)	0.77 (0.70-0.85)	0.74 (0.64-0.83)	0.70 (0.54-0.85)

Phabphal et al. submitted

OSA AND SUDEP

- In one study from Norway, 25 out of 42 cases were found dead in bed.
- Deaths were most likely to occur between midnight and 6 am
- One study of 112 PSG patients who had suffered sudden cardiac death showed that 46% of people with OSA died of sudden cardiac death in this cohort compared with 21% of those who did not suffer from OSA.

Sleep and Breathing
https://doi.org/10.1007/s11325-021-02307-1

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Obstructive sleep apnea and sudden unexpected death in epilepsy in unselected patients with epilepsy: are they associated?

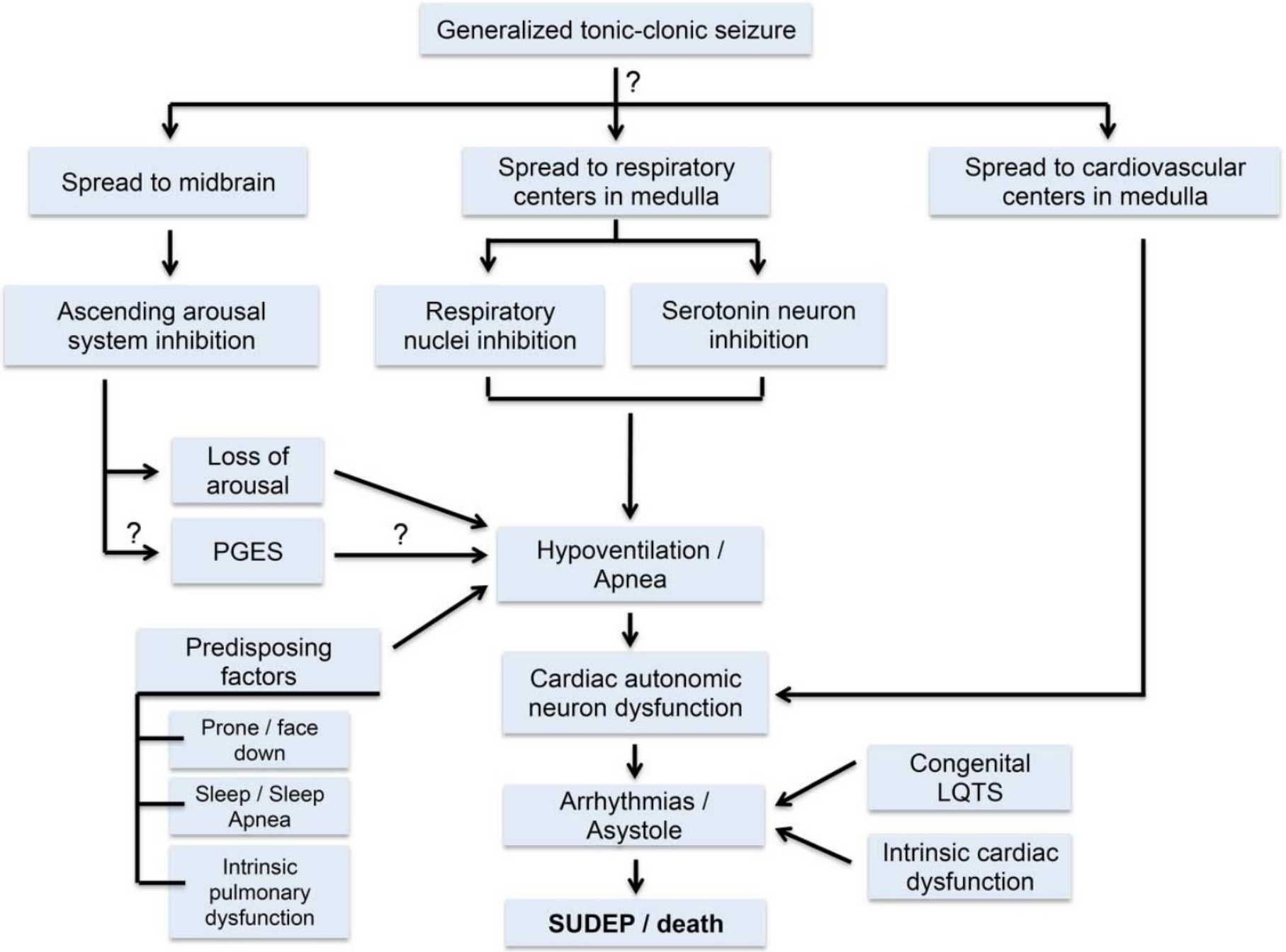
Kanitpong Phabphal[1] · Prut Koonalintip[1] · Pasiri Sithinamsuwan[2] · Krongthong Wongsritrang[3] · Thanyalak Amornpojnimman[1] · Nichanan Ekpitakdamrong[3] · Alan F. Geater[4]

Received: 6 October 2020 / R

Table 2 The association between AHI and SUDEP score

AHI	AHI median (IQR)		*p*-value
	rSUDEP-7 score < 5	rSUDEP-7 score ≥ 5	
Total	2.4 (0.7, 8.9)	1.8 (1, 4.3)	0.84
Supine	2.5 (0.9, 10.7)	1.7 (0.7, 4.8)	0.32
Non-supine	0.9 (0, 4.7)	0.6 (0, 1.2)	0.52
REM	3.2 (1.2, 11.7)	3.7 (1.8, 4.3)	0.69
Non-REM	1.9 (0.3, 7.9)	1.8(0.6, 2.6)	0.71

AHI apnea-hypopnea index, *rSUDEP-7 score* revised SUDEP risk inventory score


Generalized tonic-clonic seizure
?
Spread to midbrain
Spread to respiratory centers in medulla
Spread to cardiovascular centers in medulla
Ascending arousal system inhibition
Respiratory nuclei inhibition
Serotonin neuron inhibition
Loss of arousal
?
PGES
?
Hypoventilation / Apnea
Predisposing factors
Prone / face down
Sleep / Sleep Apnea
Intrinsic pulmonary dysfunction
Cardiac autonomic neuron dysfunction
Congenital LQTS
Arrhythmias / Asystole
Intrinsic cardiac dysfunction
SUDEP / death

CONNECTION BIOMARKER OF DRUG RESISTANT EPILEPSY

- Increasing evidence indicated that many DRE patients also present with widespread structural and functional network disruptions.
- Person-specific feature
- It is hoped that they may ultimately inform and ameliorate therapy, the scope of a biomarker is per se associative, not directly pointing to a causal mechanism.
- Effective network biomarkers
  - modeling cognitive and affective difficulties
  - surgical target and seizure network identification
  - prediction of postoperative outcomes

SUGGESTION FOR FURTHER READING

Neurological Science
https://doi.org/10.10

REVIEW ARTICL

SPECIAL REPORT | Free Access

SPECIAL REPORT

l Establishing criteria for pediatric epilepsy surgery center levels

Clinical ut
a systema
and safe r

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Lorenzo Ricci [1]
Sara Casciato [2]
Italian Neurolo

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Epilepsia
Official Journal of the International League Against Epilepsy

CRITICAL REVIEW – INVITED COMMENTARY | Open Access

Neurodevelopmental outcomes in children exposed to newer antiseizure medications: A systematic review

Rebecca Knight, Anja Wittkowski, Rebecca Louise Bromley

First published: 14 June 2021 | https://doi.org/10.1111/epi.16953

Pages: i-
Novemb
Issue Edit

Aileen McGonigal, Fabrice Bartolomei, Patrick Chauvel

First published: 11 July 2021 | https://doi.org/10.1111/epi.16994

SUGGESTION FOR FURTHER READING

VIEWS & REVIEWS

High-Frequency

What Have We Learned ar

Zhu
Dav

Neu

Received: 13 July 2020 | Revised: 29 Septem

DOI: 10.1111/epi.16753

CRITICAL REVIEW – IN

Received: 7 January 2019 | Revised: 13 February 2019 | Accepted: 14 February 2019

DOI: 10.1111/epi.14688

CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsia®

Neuroimaging and connectomics of drug-resistant epilepsy at multiple scales: From focal lesions to macroscale networks

Shahin Tavakol[1] | Jessica Royer[1] | Alexander J. Lowe[1] | Leonardo Bonilha[2] | Joseph I. Tracy[3] | Graeme D. Jackson[4] | John S. Duncan[5] | Andrea Bernasconi[6] | Neda Bernasconi[6] | Boris C. Bernhardt[1]

Connectome biomarkers of drug-resistant epilepsy

Sara Larivière[1] | Andrea Bernasconi[2] | Neda Bernasconi[2] | Boris C. Bernhardt[1]

THANK YOU FOR YOUR ATTENSION

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