

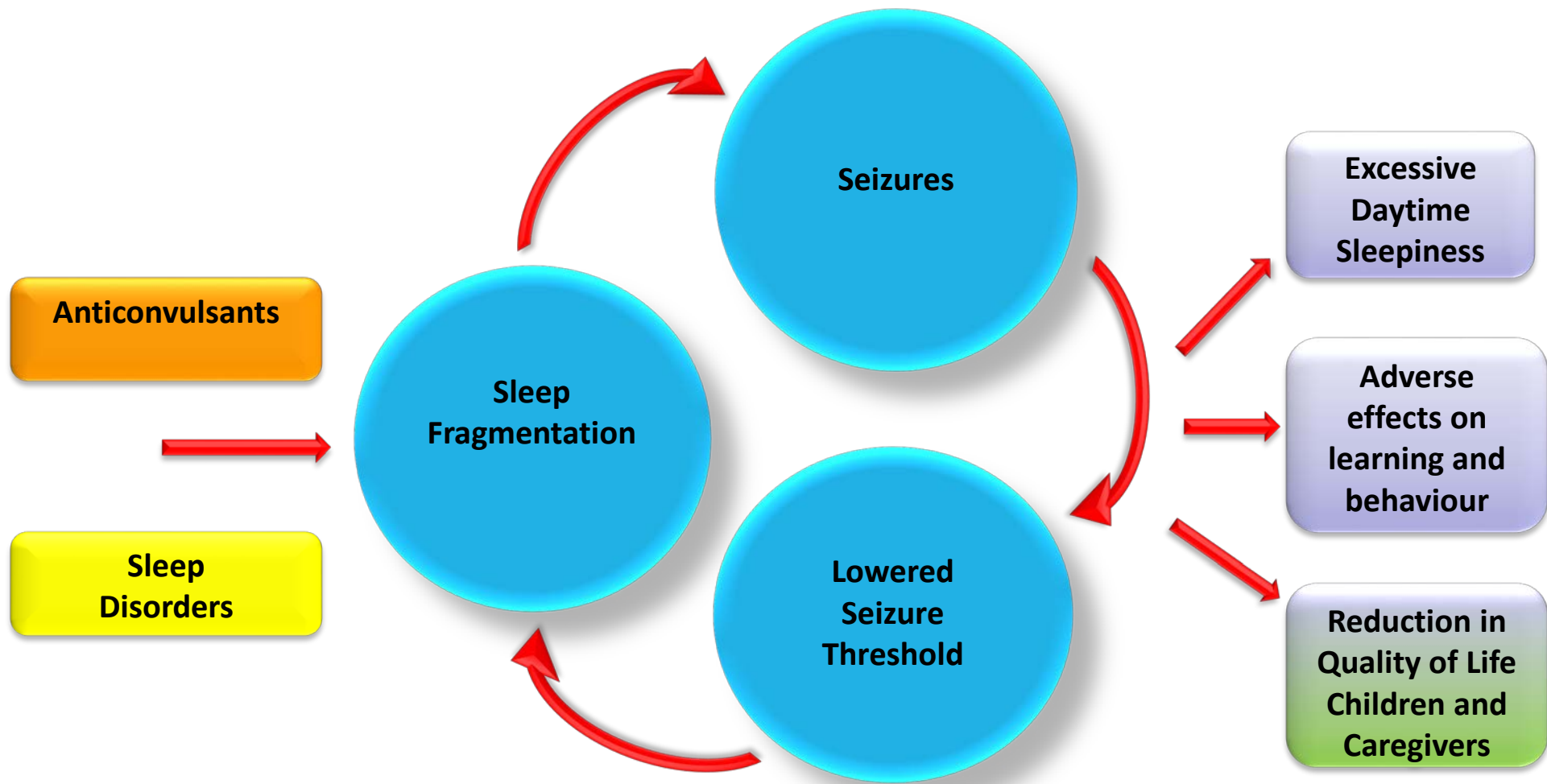
Sleep and Dravet Syndrome: Current thinking

Dravet Syndrome UK 2019

Professor Paul Gringras
Children's Sleep Medicine Department
Lifespan Sleep Medicine Group
Evelina London Children's Hospital
Guy's and St Thomas'
NHS Foundation Trust/Kings College London



- Impact of poor sleep
- Deciding the most important treatment targets
- What to treat/ How to treat
- Next generation monitoring of sleep and seizures



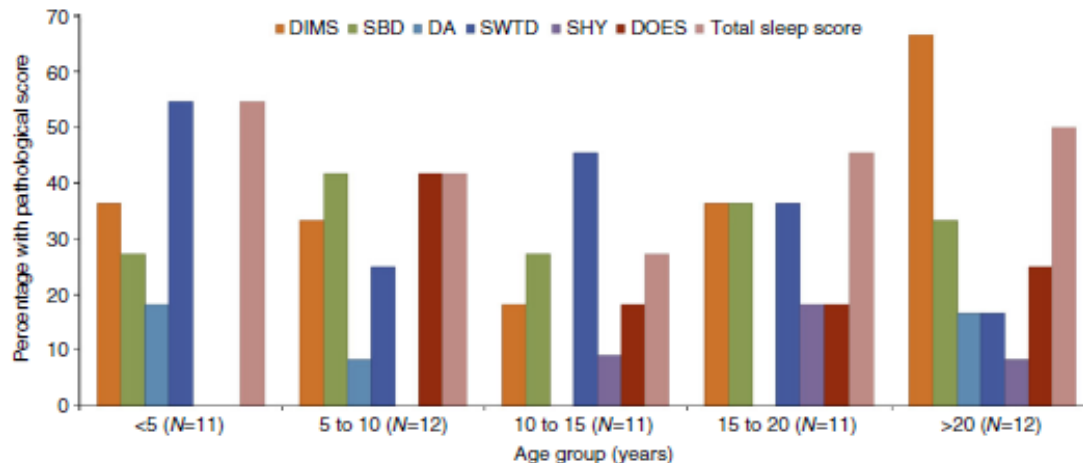
Gibbon FM, Maccormac E, Gringras P. Sleep and epilepsy: unfortunate bedfellows. Arch Dis Child. 2019.

Impact of poor sleep on parents of children with epilepsy

- Sleep duration
 - 4.5 hours (44% report never feeling rested)
- Waking
 - Three times per night
 - 7 time increase in sleep disturbances (mothers only)
- Co-sleeping/Room sharing
 - 3% control vs 16% with seizures
- Risk Factors
 - Daily seizure frequency
 - Perception of seizure frequency
 - Night seizures (70% report being concerned about night seizures)

A range of sleep disorders

- 75% of children with Dravet experience sleep disturbance
- A variety of sleep problems
 - Initiating
 - Maintaining
 - Sleep related breathing (Two children with an abnormal sleep breathing disorder score had a vagal nerve stimulator in situ.)
 - Excessive daytime sleepiness



Medication

- Twenty-two individuals (39%) took medication to assist with sleep, predominantly melatonin (n=14).
- Parents also used clonidine, trimeprazine, iron, risperidone, clobazam, fluoxetine, and 'medicinal' cannabis.
- Despite taking medication, 15 individuals had a pathological total sleep score

Quality of life

- Quality of life in Dravet syndrome was independently determined by both epilepsy-specific factors as well as comorbid impairments among the Dravet cohort
- Early onset of seizures, myoclonic seizures, and status epilepticus each independently predicted diminished HRQOL.

Child Treatment Targets(Which of these 4 are the most important -Time to vote!)

1. Child's Reported Sleep
2. Child's Objective Sleep
2. Child's alertness and learning
3. Child's behaviour
4. Child's quality of life and wellbeing
5. Nocturnal seizures

Objective treatment Goals

Measure (units)	Clinical goal (significant degree of change)	Background rationale
Sleep onset latency (minutes)	Aim for minimum 15 minutes improvement and latency <30 minutes	Parent focus group work and consensus
Total Sleep Time (minutes)	Aim for minimum 45 minutes improvement	Work by Sadeh on sleep restriction and extension in children
Wake after sleep onset (minutes)	Huge variation: Significant change 35 mins	R.A.S. van den Bossche and A.W. de Weerd Normative PSG
Sleep efficiency (%)	Aim for >85% (Significant change 6%)	R.A.S. van den Bossche and A.W. de Weerd Normative PSG
Longest sleep period	Aim for minimum 15 minutes improvement	Not experimentally or focus tested - Based on SE in study by Gringras et al

Sleep outcomes for Parent/Carer

1. Is it ethical to use medication for a child's sleep, that may not improve the child's sleep objectively, but that does improve the parental sleep and quality of life? Yes/No

If yes then please vote on which of the following are the most important.

- a. Parent's Sleep (Objective or Subjective)
- b. Parent's alertness (and risk of accidents)
- c. Parent's quality of life and wellbeing (and time off work)
- d. Family relationships

CASTLE

- The overall aim of the CASTLE study is to improve the treatment outlook and future for children affected by Rolandic epilepsy by involving children, parents and clinicians.
- The study is a programme grant supported by NIHR and will run from 2017-2023.

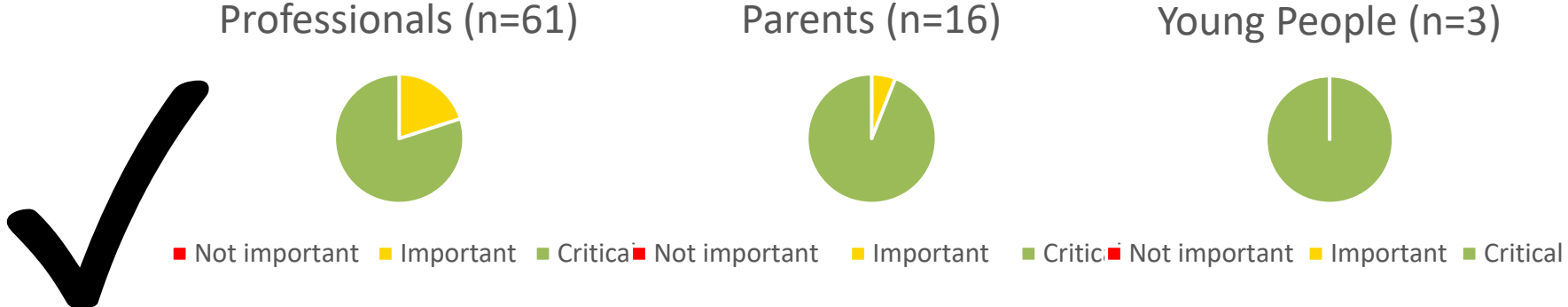
Establishing Core Outcomes

- Goal: To seek consensus (agreement) on which aspects of health and quality of life are most important to measure for children with epilepsy.
- **Step 1:** Identify candidate outcomes from papers
- **Step 2:** Delphi Survey two rounds
- **Step 3:** Review consensus and ratify core outcome set

Outcome 40

Domain: Cognition

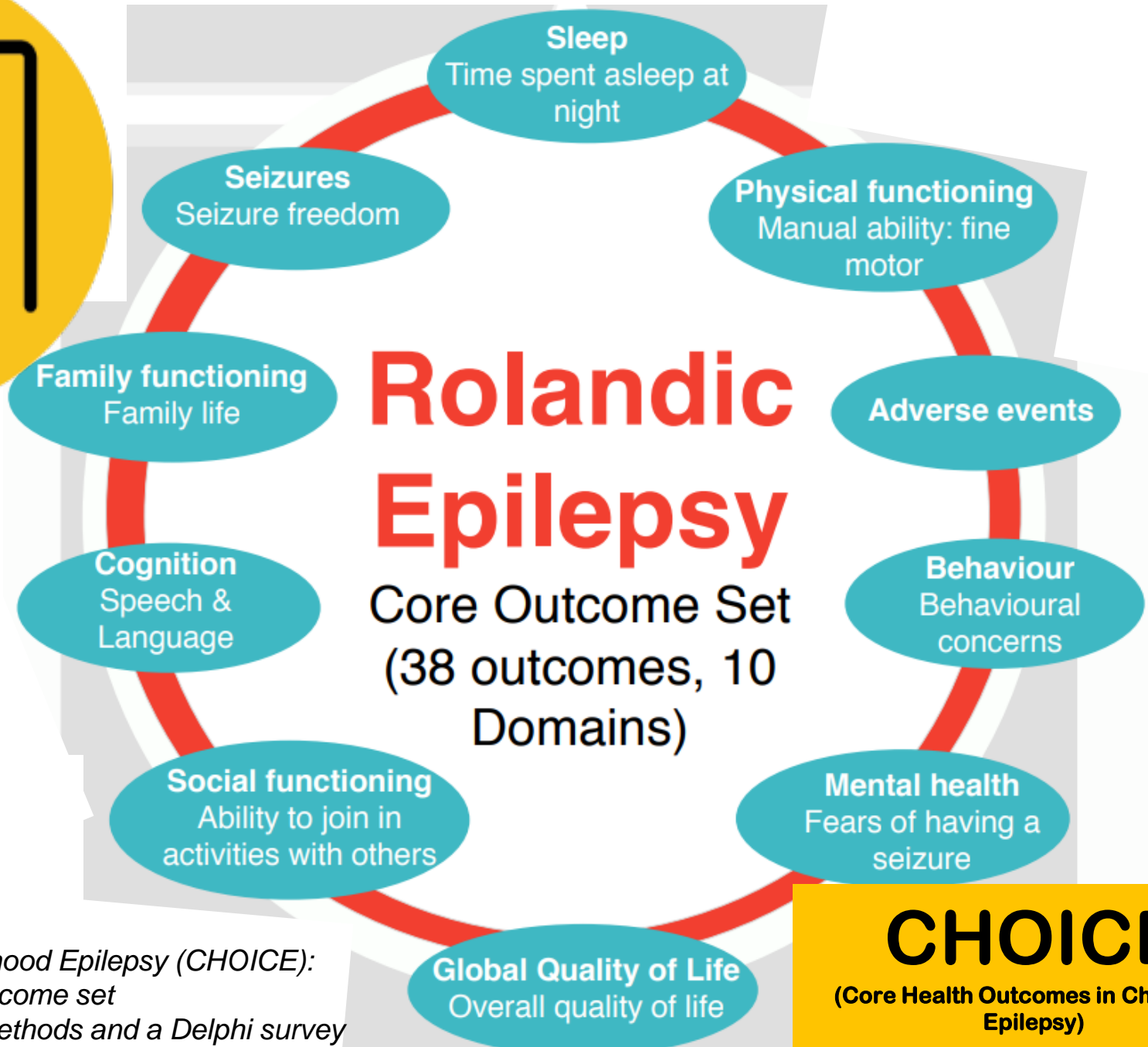
Outcomes	Professionals (n=61)			Parents (n=16)			Young People (n=3)		
	1-3 (%) (NOT THAT IMPORTANT FOR INCLUSION IN COS)	4-6 (%) (IMPORTANT BUT NOT CRITICAL)	7-9 (%) (CRITICAL FOR INCLUSION IN COS)	1-3 (%) (NOT THAT IMPORTANT FOR INCLUSION IN COS)	4-6 (%) (IMPORTANT BUT NOT CRITICAL)	7-9 (%) (CRITICAL FOR INCLUSION IN COS)	1-3 (%) (NOT THAT IMPORTANT FOR INCLUSION IN COS)	4-6 (%) (IMPORTANT BUT NOT CRITICAL)	7-9 (%) (CRITICAL FOR INCLUSION IN COS)
40. Learning	0	20	80	0	6	94	0	0	100



To discuss:

- Voted as critical for inclusion in the core outcome set.

Crudgington H, et al. Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. Epilepsia. 2019



CHOICE
(Core Health Outcomes in Childhood Epilepsy)

Crudgington H, et al. Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. *Epilepsia*. 2019

Treatment

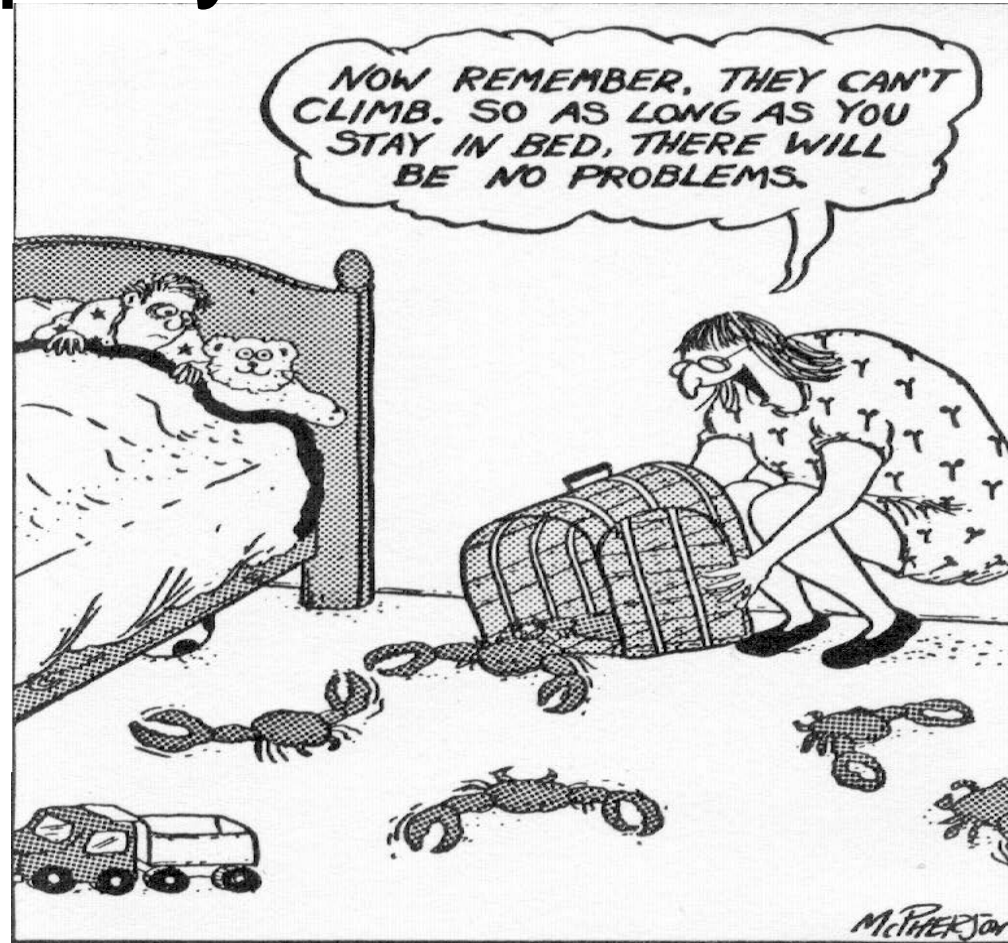
Objective measures of sleep and cognition



<http://www.cambridgecognition.com/cantab/>

What to treat and how?

Behavioural Interventions work and should always precede and then accompany medication treatments

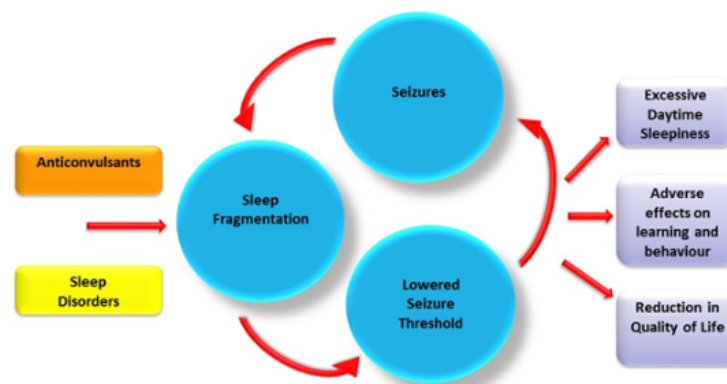


Advanced parenting techniques

A sleep e-learning programme



▾ Sleep and Seizures- a vicious cycle?



Have a look at the picture showing the sleep and seizure vicious cycle.

A lot of different things can affect your child's sleep quality and their seizure control. Sometimes they work together to make things worse and we call this a vicious cycle.

Because brain electrical activity is really strong and rhythmic during certain stages of sleep, it means some seizures occur more commonly during sleep.

Night-time seizures themselves can worsen sleep quality, and poor sleep quality itself is a trigger for seizures.

Finally some antiepileptic drugs can unfortunately worsen sleep.

For all these reasons we think that getting as good sleep as possible is really important for children with epilepsy and this module has some advice that we hope can help.

▸ Sleep and Seizures- some common problems

▸ Seizures, sleep and risks

▸ Seizures and sleep fears for parents

▸ Seizure Medications and Sleep

Pharmacological Treatments

Review

When to use drugs to help sleep

P Gringras

Correspondence to:
Paul Gringras, Evelina Children's
Hospital, St Thomas' Hospital,
Lambeth Palace Road,
London SE1 7EH, UK;
Paul.gringras@gstt.nhs.uk

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ABSTRACT

Paediatric sleep medicine is a relatively new but important and rapidly growing field. It is increasingly recognised that many "adult" sleep disorders begin in childhood where the consequences of missed diagnoses can be devastating. Adequate training of all health care professionals and careful eliciting of symptoms remains the first step in ensuring accurate and timely diagnoses. Although behavioural approaches play a huge role in paediatric sleep medicine, at times severe sleep disorders also

approaches. However, effective
gical and pharmacological
across the age ranges. The use
logical interventions for paediatric
lacks a robust evidence base and
unlicensed or off-label medication
have been small and poorly
the situation is now improving
provides little solace to a desperate
to cope with a child's intolerance.

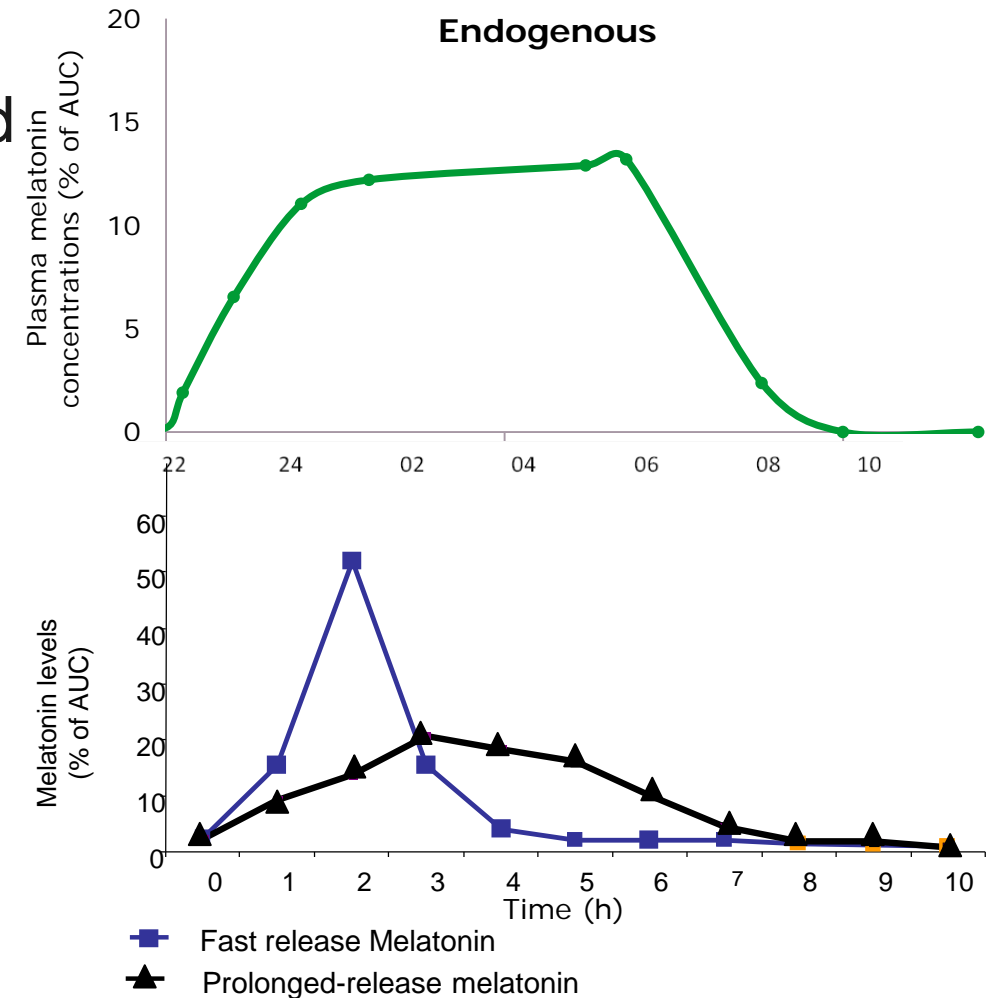
Arch Dis Child 2008;**93**:976–981.

Mindell et al Pediatrics. (2006); Felt B. T., et al. Neurol Clin Pract. (2014)
Hack S, et al. J Child Adolesc Psychopharmacol (2001)
Owens JA et al. J Clin Sleep Med (2005)

Prolonged release melatonin in child appropriate formulation

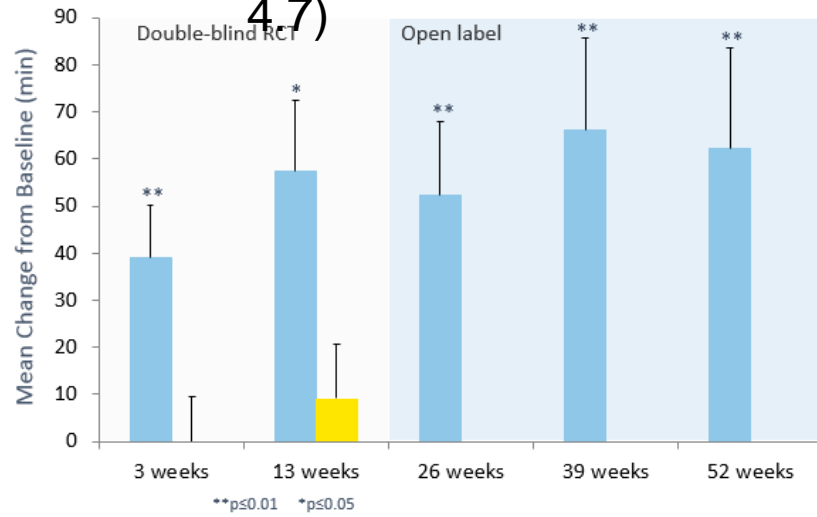
Immediate Release melatonin (IRM) has a rapid onset to high levels and rapid decline

Prolonged Release melatonin (PRM) mimics the endogenous profile of melatonin

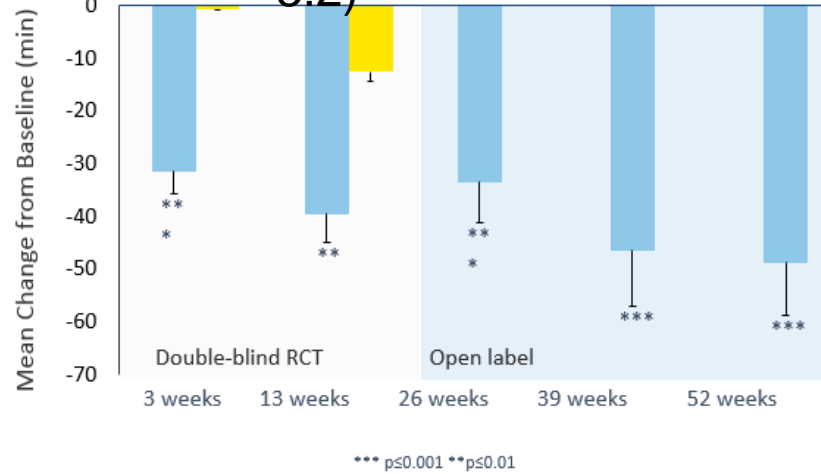


Impact of PR Melatonin on Child's Sleep

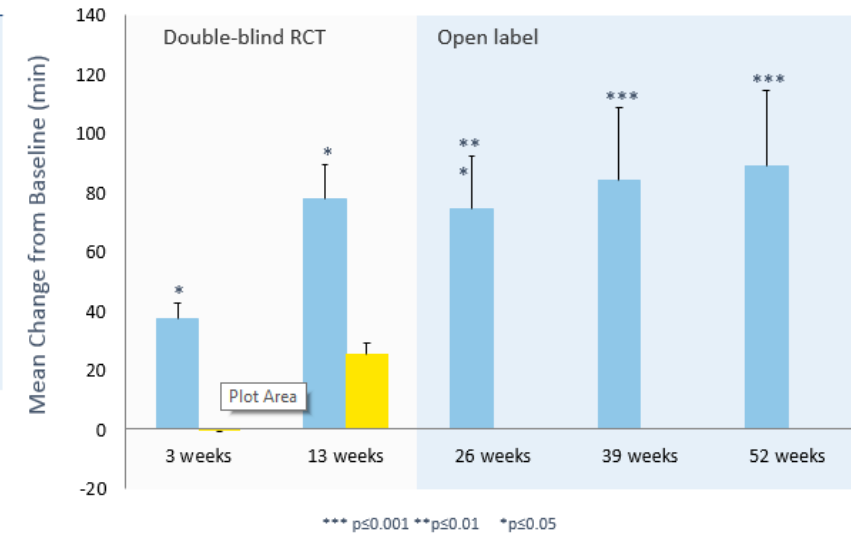
Total Sleep Time (NNT 4.7)



Sleep Latency (NNT 3.2)



Longest sleep duration



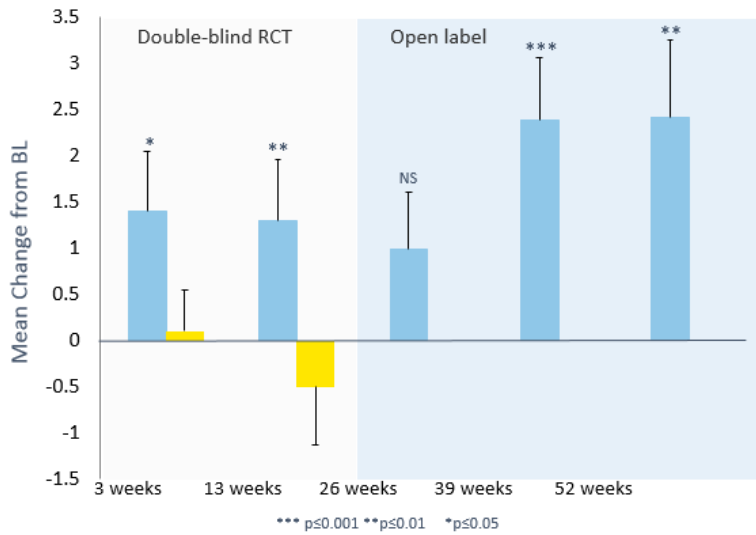
■ Ped PRM
■ placebo

Gringras P et al
J Am Acad Child Adolesc Psychiatry. 2017

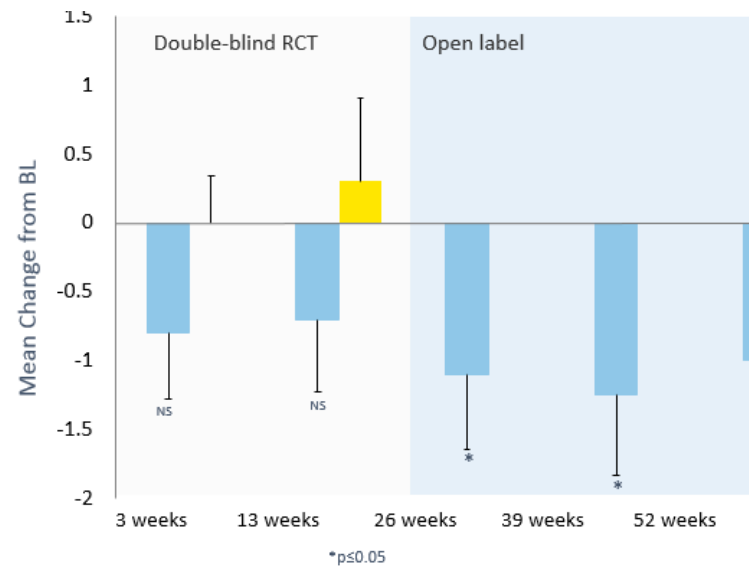
Maras, Schroder, Malow, Findling, Breddy, Nir, Zisapel, Gringras.
J Child Adolesc Psychopharmacol. 2018

Secondary outcomes

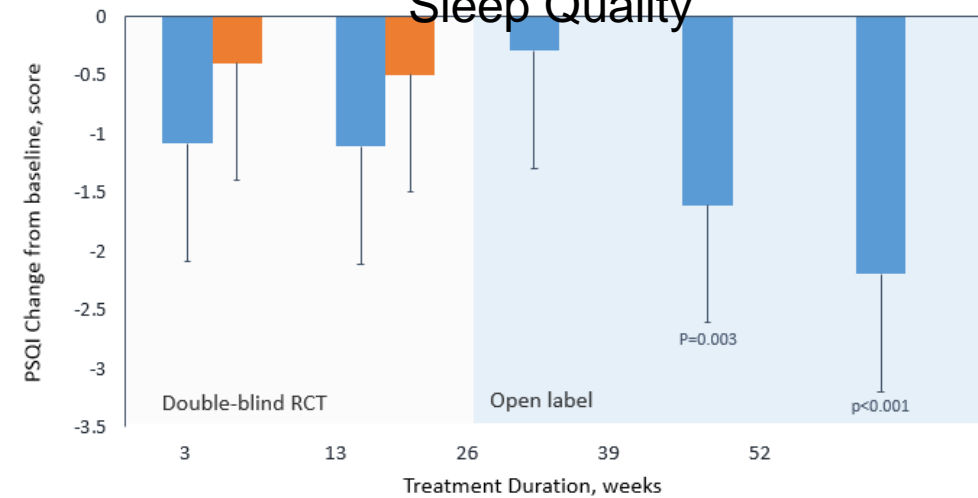
WHO-5 (12 months)



ESS (12 months)



PSQI-Parents Sleep Quality



Maras, Schroder, Malow, Findling, Breddy, Nir, Zisapel, Gringras. *J Child Adolesc Psychopharmacol.* 2018

Epilepsy and Sleep Disordered Breathing- Risk Factors

- Children in General Population
 - Increased BMI
 - Large adenoids/tonsils
 - Age 3-5 years
- Children with Epilepsy
 - Poor seizure control
 - Drug polytherapy
 - Vagus nerve stimulation (15-90%)
 - *Malow 2000 Neurology*

Prevalence of OSA in Children with Epilepsy

- PSG Studies
 - Obstructive sleep apnoea 20-80%
 - Central Apnoea 6%
 - Hypoventilation 6-12%
- But methodological problems
 - Comorbidities
 - Small studies
 - BMI and adenotonsillar hypertrophy not always recorded (but no association to date)

Gogou 2015 Sleep Breath

Impact of OSA on children with epilepsy

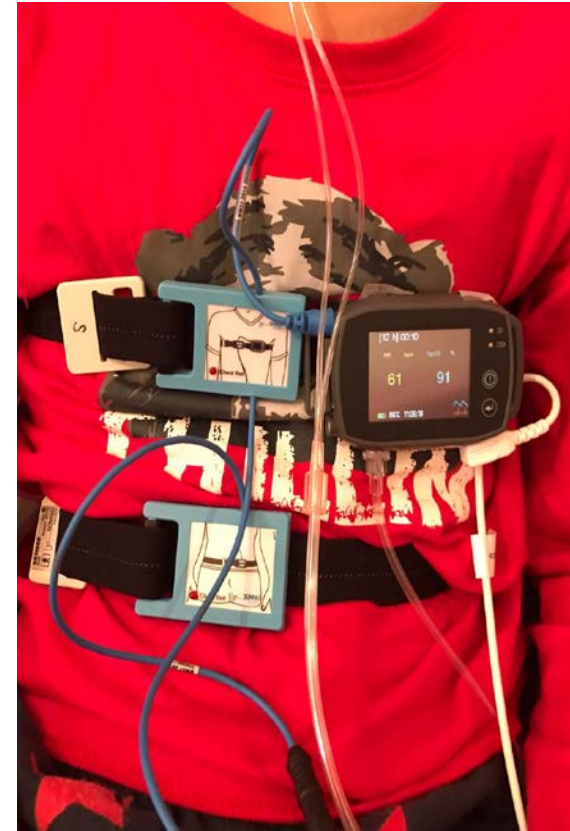
- Increased arousals
 - Less REM
 - More fragmentation and deprivation
- Hypoxia
 - May trigger seizures
- Cognition
 - Lower executive functioning
 - Lower phonological processing
 - Worse learning and memory
 - Worse daytime behaviours
 - *O'Brian 2004 J Sleep Res / Honaker 2009 Dev Neuropsychol*
- SUDEP ?

Role of oximetry

- NOT a diagnostic test by itself
- Low sensitivity
- Can confirm a clinical impression
- Can help stratify severity
- Technical considerations



Home cardiorespiratory



Obstructive Sleep Apnoea in Epilepsy

Treating OSA/Seizures

- OSA
 - 3 months post T and A 70% reduced seizure frequency and 37% seizure free
 - Segal 2012 Paed Neurology/ Malow 2003 Sleep Med
- Seizures
 - One study showing improvement in OSA post epilepsy surgery
 - Zanzmera 2013 Sleep Med
 - Choosing AED with less impact on sleep?
 - Lowering VNS stimulation frequency?

Considering OSA in children with epilepsy

During the night does your child ever:

G gasp or choke?

A (apnoea) stop breathing?

S snore loudly?

P (perspire)?

- Consider cardiorespiratory study:
 - Suggestive history of OSA
 - Risk factors
 - Prior to VNS
 - Prior to epilepsy surgery

AED and Sleep Architecture

- All AED have some impact on sleep
- Limited number of studies that have objectively evaluated sleep architecture
- Ethics of healthy volunteer studies and problems determining true AED effect independent of effects of epilepsy
- Separating impact on sleep timing, duration, quality or stages

Jain 2014 Epilepsia

SUDEP and Wearable Devices

- ‘Reliable GTCS detection might help physicians optimize antiepileptic treatment, which could in turn reduce the risk of SUDEP.’
- Novel ambulatory data
 - Realtime seizure alert
 - Electrodermal
 - Heart rate
 - Oxygen saturations
- Biomarkers still unhelpful
 - Heart rate variability
 - Periictal cardiorespiratory dysfunction
 - Postictal EEG suppression

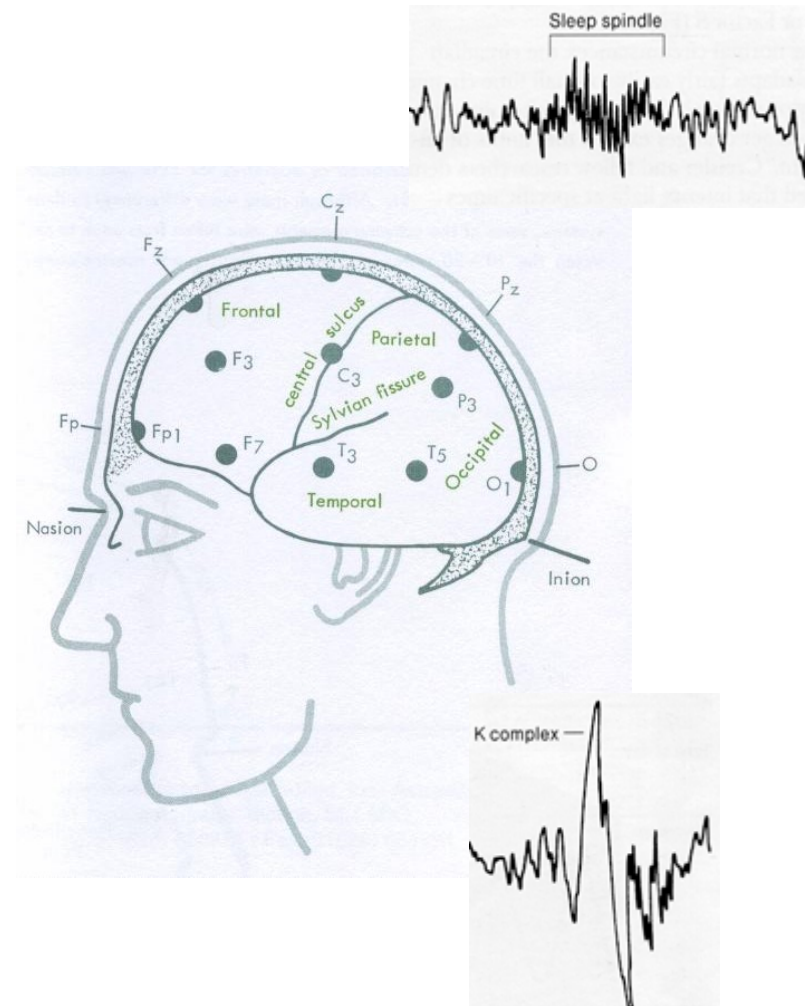
Ryvlin P Epilepsia 2018

Ryvlin Current opinions in neurology 2019

Van Ness Are Seizure Detection Devices Ready for Prime Time? Epilepsy curr 2019

New Technologies

Polysomnography



Polysomnographic Shrinking Technology

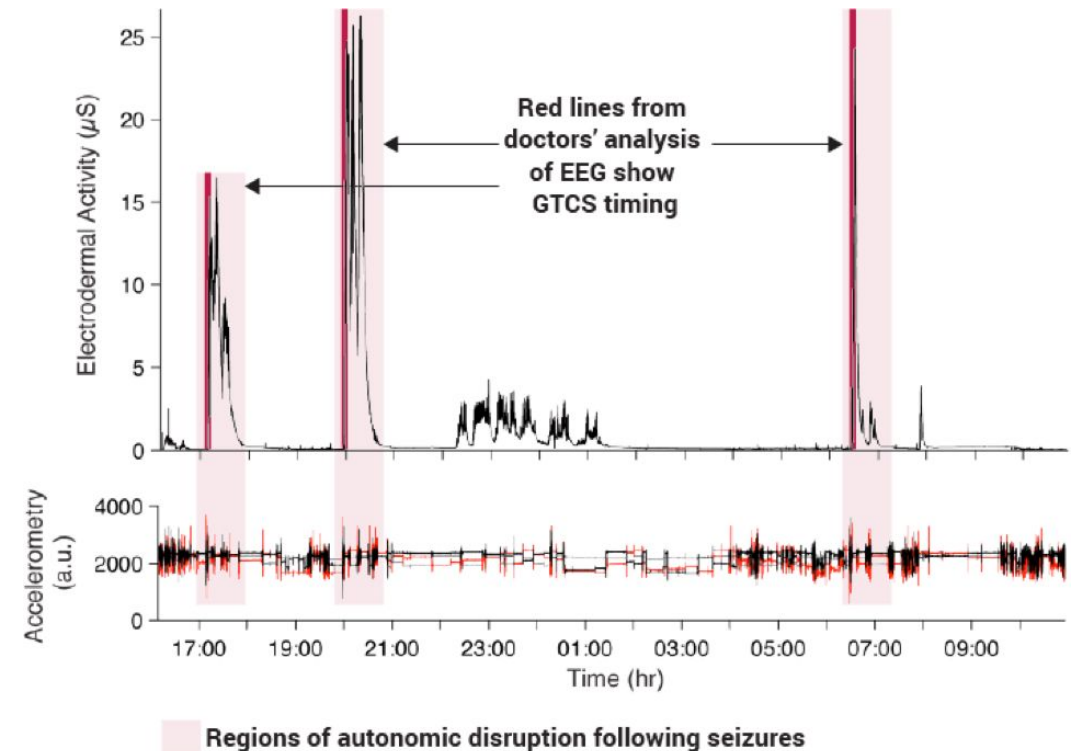
- ‘Dreem miniaturized the PSG and transformed it into a comfortable sleep experience.’
- Accelerometer
- Position sensor
- EEG electrodes
- Oximeter/Heart Rate
- ? Potential for home overnight monitor



Embrace 2



- Embrace2 has been cleared by the FDA as a medical wearable for adults and children ages 6 and up
- Embrace is designed to detect possible generalized tonic-clonic seizures lasting longer than 20 seconds.
- Other non-convulsive seizure types currently cannot be detected by Embrace2.
- Potential as
- Electrodermal activity correlates with post-ictal generalized EEG suppression (PGES) .



Poh, M. Z., et al (2012 b). Autonomic changes with seizures correlate with postictal EEG suppression. Neurology, 78(23)

Seizurelink

- ‘Small and lightweight, the SeizureLink Monitor sticks to the top of your biceps muscle to alert Caregivers about sustained tonic muscle activity.’



Epicare mobile

‘The sensor detects tonic clonic seizures and is suitable for anyone over 10 years old.’



The End

Any Questions?

Paul.gringras@gstt.nhs.uk

@sleepprof