Targeted Therapies and New Options for Epilepsy

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FROM THOUGHT TO ACTION

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Epilepsy

- Frequency ~ 4-10/1000 individuals per year
- If not treated may be associated with progressive impairment of cognition, psychosocial and neurological function, decreased QOL
- Epilepsy may be associated with severe consequences - social stigmata, SUDEP, ..
- Many new drugs, with better tolerance, safety profiles, fewer drug interactions, simpler pharmacokinetics
- However ~35% not totally controlled

Classification of the Epilepsies 2017

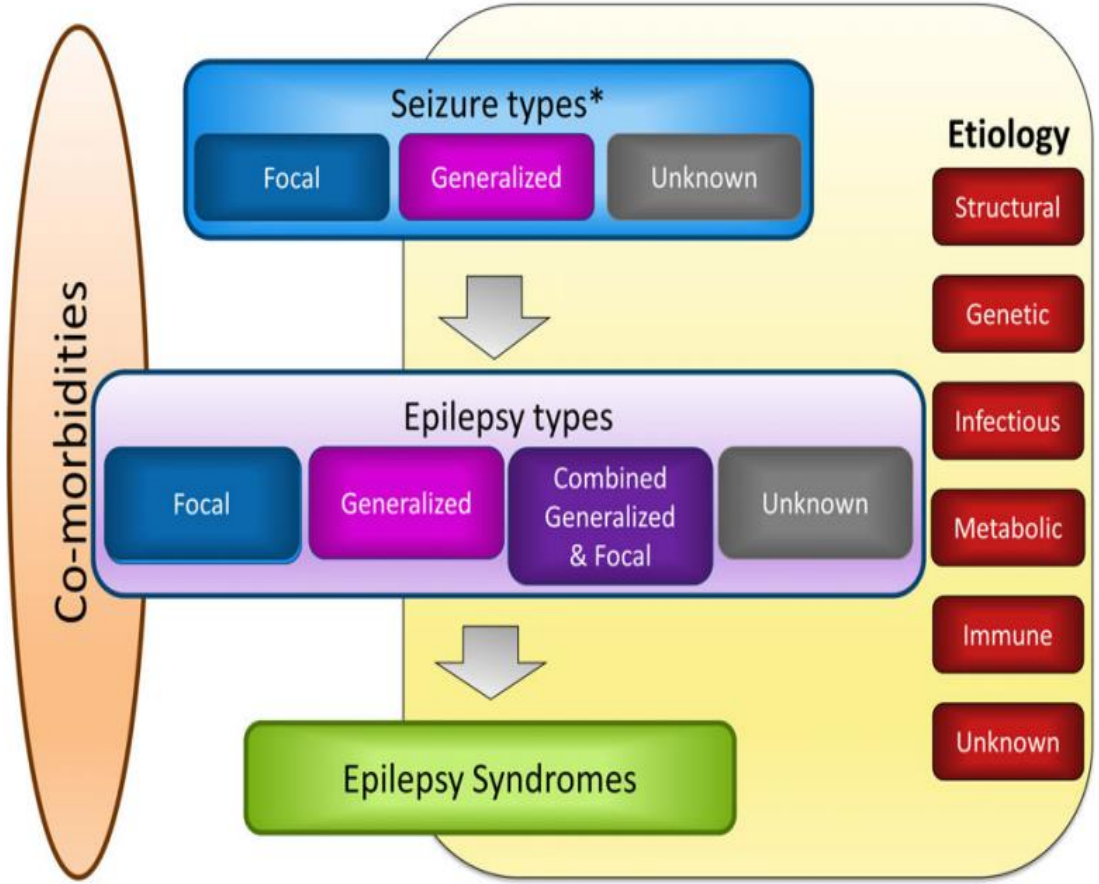


Figure 1.
Framework for classification of the epilepsies. *Denotes onset of seizure.
Epilepsia © ILAE

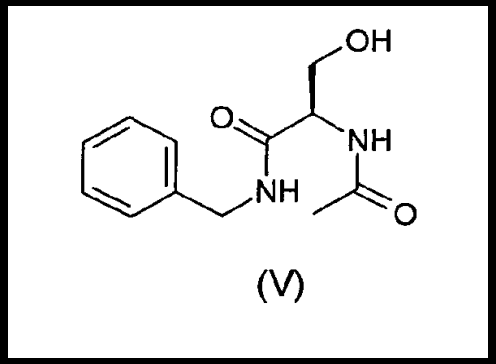
Targeted Therapies and New Options for Epilepsy

- New drugs
  - seizure/epilepsy or syndrome specific
  - Aetiology specific
- Novel approaches
  - Antiseizure vs antepileptogenic interventions
  - Immune Modulation
  - Gene and Stem Cell Therapy
  - Non Invasive Brain Stimulation
- Diets: Atkins, MAD, Low Glycaemic Index
- Surgery

New AEDs in Epilepsy

- Brivaracetam
- Lacosamide
- Rufinamide
- Retigabine
- Perampanel

- Kanner et al, Neurology 2018, 1&2



(R)-2-Acetamido-N- benzyl -3- methoxypropionamide

Functionalised AA – Analgesic & Anticonvulsant property

Lacosamide -

MOA

Selective enhancement of slow inactivation of VGSC

Collapsing response mediator protein (CRMP2) ??

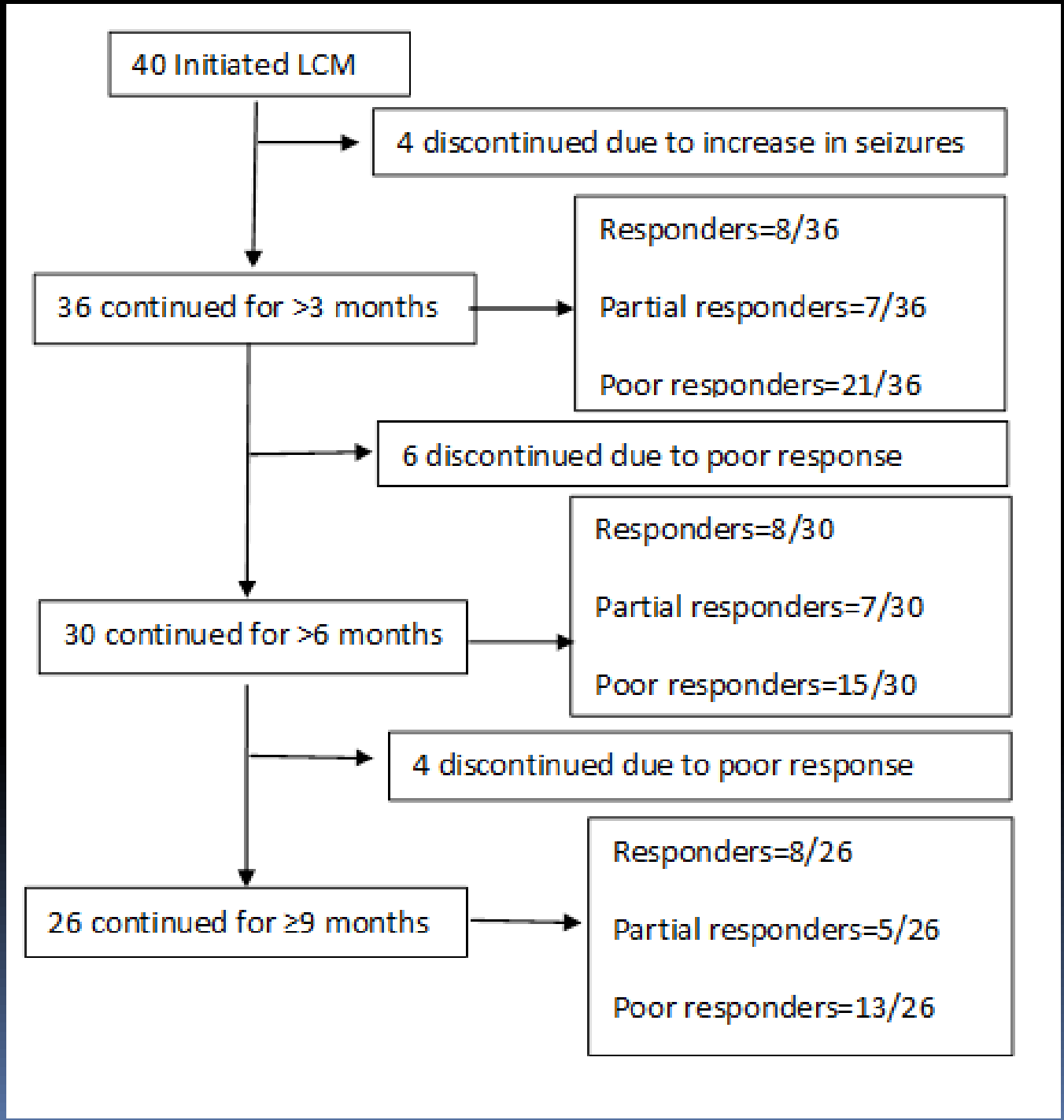
- Ben-Menachem, Epilepsia. 2014
- Doty et al. Neurotherapeutics . 2007

Lacosamide

- Its efficacy with focal seizures is confirmed in open label and placebo controlled trials.
- In CWE response rates vary from 20 – 85%.
- 18-69% of adult patients achieved at least 50% reduction in seizure frequency, and 1.7-26.2% achieved seizure freedom.
  - Yorns et al, J of Child Neurol 2014. Paquette et al, Seizure 2015.
  - Kanner et al, Neurology 2018. Hoy, CNS Drugs 2018. Rosati, et al, Epilepsia 2018.

LCM as adjunctive therapy in TREC: our experience Journal of Child Health and Paediatrics. 2015

- **40** children, age range: 2-19 years.
- All had abnormal EEGs and 36 had abnormal neuroimaging.
- All children failed > 2 AED trials, in addition
  - 9 had trialed the ketogenic diet
  - 5 the vagal nerve stimulator and
  - 11 had failed resective epilepsy surgery.
- Median dose was 5.7mg/kg/day
- Median duration of LCM therapy - 9 months


40 Initiated LCM
4 discontinued due to increase in seizures
36 continued for >3 months
Responders=8/36
Partial responders=7/36
Poor responders=21/36
6 discontinued due to poor response
30 continued for >6 months
Responders=8/30
Partial responders=7/30
Poor responders=15/30
4 discontinued due to poor response
26 continued for ≥9 months
Responders=8/26
Partial responders=5/26
Poor responders=13/26

LCM in TREC

- RR was seen in 20%
  - with persistence of RR in 8/36, 8/30 and 8/26 children on LCM at 3, 6 and 9 months follow-up.
- Two children became seizure free.
- Responses in children occur early; all children who had a 50% reduction of seizures on LCM did so within the first three months of therapy.
- Retention on LCM was 65% at 9 months.
- LCM was well tolerated with minor side effects in 7, no child discontinued LCM because of side effects.

Lacosamide

- In Status Epilepticus
- In Generalised Epilepsies

LL-Epilepsy

- Onset : 18 months of age
- Sz types : drops,
  complex partial seizures,
  head drops with extension of arms - asymm. tonic events,
  clonic events - focal or bilateral, rare myoclonic events.
- Sz frequency: ~3 clusters of events/day, lasting upto an hour each, consisting of 3-4 more severe events followed by lots of little ones.
- Trialled multiple AEDs
- ECS of ? LGS - what new drug may be particularly useful?

? Which new drug

- Video +EEG

EEG

EEG

Rufinamide

- A triazole derivative
- MOA: prolongs the inactive state of neuronal sodium channels and limits Na dependant action potential firing
- Adjunctive therapy in children with seizures associated with Lennox Gastaut Syndrome, may also be used with partial szs
- 25-60mg/kg/day
- In double blind trials significantly reduced the number of drop attacks, and total szs in cf with placebo.
- Somnolence, vomiting, diarrhoea, URTIs, infections, decreased apetite, rash – side effects
  - McCormick, Pharmacoeconomics. 2012, Ben-Menachem, Epilepsia. 2014

Safety and retention rate of rufinamide in 300 patients: a single pediatric epilepsy center experience.

Thome-Souza S et al, Epilepsia, 2014

- 300 with a median age of 9.1 years, median FU – 9 months
- Epilepsy aetiology was classified
  - as genetic (23.7%), structural/metabolic (41%), and unknown cause (35.3%). Sz reduction greater in genetic aetiology
- Overall, rufinamide led to a median sz frequency reduction of 59.2%.
- Rufinamide was discontinued in 36.7% :
  - 21% -unsatisfactory response, 15.7% - side effects, and in 6% -both.
- Most common adverse effects were sleepiness, vomiting, mood changes, nausea, and loss of appetite.
- Median time to loss of efficacy was 11.6 months (range 3-28 months).

Our experience

- Twenty patients were treated with Rufinamide on a compassionate use basis with SAS approval, between 2012 – 2018, at PMH.
- T he patient population was complex, with a large number of seizure types and a high burden of previous AEDs and non-pharmacological Rx .
- The overall response rate (>50% reduction) to Rufinamide was 25%, with the strongest response in patients with LGS.
- Adverse events (AE) were seen in four patients and all AE were mild.
- Rufinamide was discontinued:
  - in 7 due to poor response; in 2 due to an increase in seizure frequency; in one patient due to an AE and poor response; and in one patient due to an AE.

Rufinamide: specific drug for LGS and other EEs?

- Rufinamide is effective in decreasing the seizure frequency in the Lennox-Gastaut syndrome especially tonic and atonic seizures.
- It might consequently be preferred to other drugs as a second-line treatment for LGS when drop-attacks are frequent.
- The mean responder rate in the published studies is 38% with seizure freedom achieved in 2.4% of patients.
- Rufinamide has shown some efficacy in epileptic encephalopathies other than LGS. It can be also effective as adjunctive therapy in children and adolescents with drug-resistant partial seizures
- Coppolla et al, Eur J Peadiatr Neurol 2014

Rufinamide in children and adults in routine clinical practise

- 58 patients (40 male, age range 7-57 years),
  - 25 of whom were diagnosed with LGS, 12 with other epileptic encephalopathies 21 of whom were diagnosed with focal epilepsies
  - The mean daily dose was 32.0 mg/kg in children & 24.7 mg/kg in adults,
  - and the most commonly used concomitant antiepileptic drugs were LEV and VPA.
- Rufinamide was discontinued in 25 patients during 1-year follow-up, most common reason was lack of effectiveness
- Frequency of GTCS was significantly reduced from baseline at 6 and 12 months (P = 0.001), both in FE and GE.
- Significant seizure frequency reduction from baseline was observed at 12 months (P = 0.01) for tonic/atonic seizures and at 6 months (P = 0.001) for focal seizures.
- Side effects in 21 : nausea, vomiting and weight loss being most frequent.

- Rufinamide was well tolerated and was effective in reducing frequency of generalized tonic-clonic, tonic/atonic and focal seizures in both children and adults with severe refractory epilepsies, primarily LGS.
- Jaraba,et al, Acta Neurol Scand 2017

Perampanel

- First of it's kind
  - Selective non-competitive antagonist of excitatory post synaptic AMPA glutamate receptors
- AMPA receptors thought to play a significant role in the development of seizure activity
- They bind both glutamate and ligand gated cation channels.
- Faulkner and Burke. Expert Opinion 2013. Ben-Menachem. Epilepsia 2014

Perampanel

- Adjunctive therapy for partial seizures
- Very long half life – 66-90 hours, once daily dosage.
- 4-12 mg/day
- Dizziness and somnolence - common side effects
- Ataxia, fatigue, disturbances of gait, headache, weight gain, neuropsychiatric, ? Potential for abuse
- OXC, CBZ, PHT reduce serum levels of Perampanel

Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analsis of three phase 111 studies. Steinhoff et al. Epilepsia 2013

- 1478 patients from 3 studies
- Dosages: 2-12 mg/day
- Median change in partial szs: 23-29%
- 50% responder rates were 28-35% (placebo:19.3%)
- Perampanel generally well tolerated
- Most TEAEs were mild to moderate
- No deaths and no meaningful change in lab values, ECGs or vital signs.

- Perampanel is a broad-spectrum AED that may be a useful with various seizure types, including PGTCS
- Tolerability and effectiveness of PER in highly drug-resistant patients with different epilepsy syndromes and aetiologies has been shown in several studies.
- Response better / adverse events higher in females?
- May have anti-inflammatory, anti-apoptotic and antioxidant properties, may be neuroprotective

- Tremblay et al, Epil Behaviour 2018. Nakajima et al, Neuroscience 2018. Youn et al, J Clin Neurol, 2018. Potschka et al, Epilepsia 2018. Morano et al, J Clin Neuroscience 2018, Krauss et al, Epilepsia, 2018

Retigabine

- first neuronal potassium (K(+)) channel opener AED
- KCNQ channels are active at the normal cell RMP and contribute a continual hyperpolarizing influence that stabilizes cellular excitability.
- RTG increases the number of KCNQ channels that are open at rest and also primes the cell to retort with a larger, more rapid, and more prolonged response to membrane depolarization or increased neuronal excitability.
- RTG amplifies the natural inhibitory force in the brain, acting like a brake to prevent high levels of neuronal epileptiform activity, and hence influences initiation and propagation of seizures.
- can stabilize the open form of KCNQ2-5 channels
- **subtype selective modulator of GABAA receptors**
- Treven et al, Epilepsia 2015. Gunthorpe et al, Epilepsia 2012. Rheims & Rivlin, Expert Review Neurotherapeutics, 2013.

Retigabine

- Relevant particularly for BFNS – KCNQ2/3
- Add on therapy in refractory focal seizures
- Broad spectrum of action
- Potential for drug interactions low.
- 8 hourly dosage
- Max: 1200 mg/day in adults
- Common side effects: dizziness, fatigue, cconfusion, somnolence,dysarthria, ataxia, diplopia, urinary tract retention and infection

Retigabine

- Serious side effect : development of blue hue to the skin and retina after long term use
- The skin discolouration may be reversible
- Caution: wait and see.
- GSK has discontinued Retigabine in June 2017

- Mathias, Epilepsy Behaviour case report 2017. Clarke et al, Ther Adv Drug safety 2015, Kolnick et al, JAMA Dermatol, 2014

Brivaracetam

- Brivaracetam (BRV) is a new AED, structurally related to LEV , has 15 to 30-fold increased affinity for the same molecular target, namely the SV2A ligand, ? also partial antagonist on neuronal voltage-gated sodium channels
- adjunctive treatment for focal epilepsy
- potential efficacy for PGE
- linear pharmacokinetics
- extensive metabolism into inactive compounds, mainly through the hydrolysis of its acetamide group, 95% excreted in urine
- No significant interactions with other AEDs. AE mild to mod and often transient
- BRV has a half-life of approximately 8-9 hours and it is usually given twice daily, dose: 50 -200mg/day
- Mula Exp Rev Neurother, 2014. Rivlin et al, Epilepsia 2014.Biton et al, Epilepsia 2014. Klein et al, Exp Opin Pharmacother., 2016. Hoy, CNS Drugs 2016

BRV

- Immediate switch from LEV to BRV, at a conversion ratio between 10:1 to 15:1 is feasible, and might alleviate the behavioural side effects associated with LEV.

- May have role in focal and idiopathic generalised epilepsies

- Strzelczyk et al, Exp Rev Clin Pharmacol, 2016

Rich, Lush and Green

An ancient treatment for many ailments

- Cannabis
- THC: Tetrahydrocannabinol major psychoactive ingredient
- CBD: Cannabidiol non-psychoactive

Cannabidiol- critical review and commentary

- Cannabis and THC are anticonvulsant in most animal models but can be proconvulsant in healthy animals.
- CBD has neuroprotective and anti-inflammatory effects in humans
- May work thru X mechanisms:
  - ENT -equilibrative nucleoside transporter, orphan G-protein-coupled receptor GPR55, TRP – transient receptor potentials , 5HT1a receptor, alpha 3 and 1 glycine receptors, PPAR, antioxidant properties.
- Is well tolerated
- Studies in epilepsy mostly small & methodologically ltd – results often inconclusive. RCTs now for some EEs
- Devinsky et al, Epilepsia 2014, Cilio et al. Epilepsia 2014.

Cannabidiol: Promise and pitfalls

- Cannabinoid system can regulate epiletogenesis
- Mediated thru G protein coupled receptors, cannabinoid Type 1 (**CB1**) and CB2
- CB1 when activated inhibits synaptic transmission via action on voltage gated Ca and K channels, modulating epileptiform activity
- CBD may act at CB1 receptors to inhibit glutamate release.
- CB1 receptor expression upregulated at GABAnergic synapses and down-regulated at glutaminergic synapses in epilepsy , contributing to lowering of sz thresholds.
- CBD may also act on transient receptor potential channels (TRP) that are involved in modulation of intracellular Ca, this may be how it is neuroprotective.
- Welty et al, Epilepsy Currents. 2014

CBD

- Mathern et al, Epilepsia, 2015
  - **Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey**

- **Perucca , J of Epil Res 2017: Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?**
  - Three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD
  - in patients with Dravet syndrome and Lennox-Gastaut syndrome.
  - In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome.
  - For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes
  - ?direct drug action or due to drug interaction with particularly a marked increased in plasma levels of N-desmethylclobazam, the active metabolite of clobazam

- Haussman-Kedem et al. Brain a and Dev 2018
  - **Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents - An observational, longitudinal study. ~ 50 % had > 50% reduction in sz frequency**

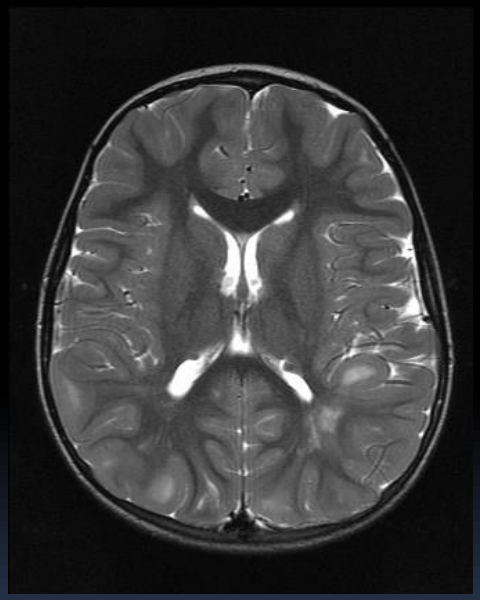
- Reithmeier et al, BMJ 2018
  - Study design of Phase 1 trial in treatment resistant epileptic encephalopathy , using herbal extracts.
  - This study will provide the first high quality analysis of safety of CBD-enriched Cannabis herbal extract in pediatric patients in relation to dosage and pharmacokinetics of the active cannabinoid

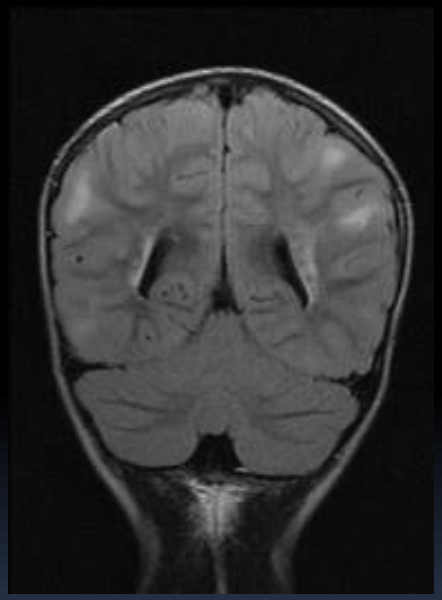
TREC with developmental stagnation

EEG

EEG

Child with Refractory Epilepsy

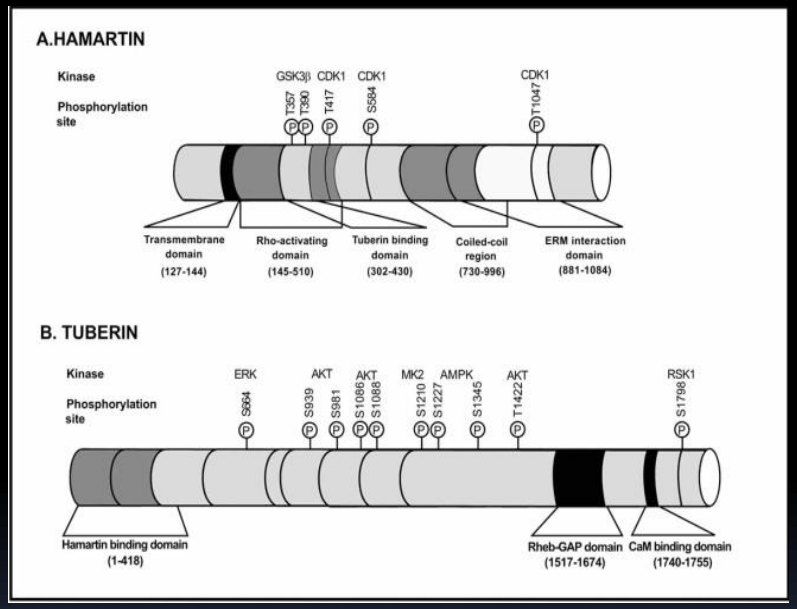




Tuberous Sclerosis Complex

- Birth rate of 1 in 6000,
  - population based studies had indicated 1 in 12-14000 children under ten
- Diagnosis: major and minor features. Roach et al, 1998
- Sometimes an antenatal diagnosis is able to be made based on cardiac and brain lesions
- Most features of TS become evident in childhood
- Early diagnosis makes early treatment and interventions possible

TSC



Overall mutation detected rate is 85-90%

Autosomal dominant – Two-thirds of patients have sporadic mutations.

TSC1 (9q34) encodes hamartin and TSC2 (16p13.3)encodes tuberin

Tuberin and hamartin form an intracellular complex that is part of many cell processes such as cell cycle progression, transcription and translation control and nutrient uptake

Independantly of the complex they also bind to several other proteins – physiological fn?

Cell signalling pathways and the hamartin tuberin complex

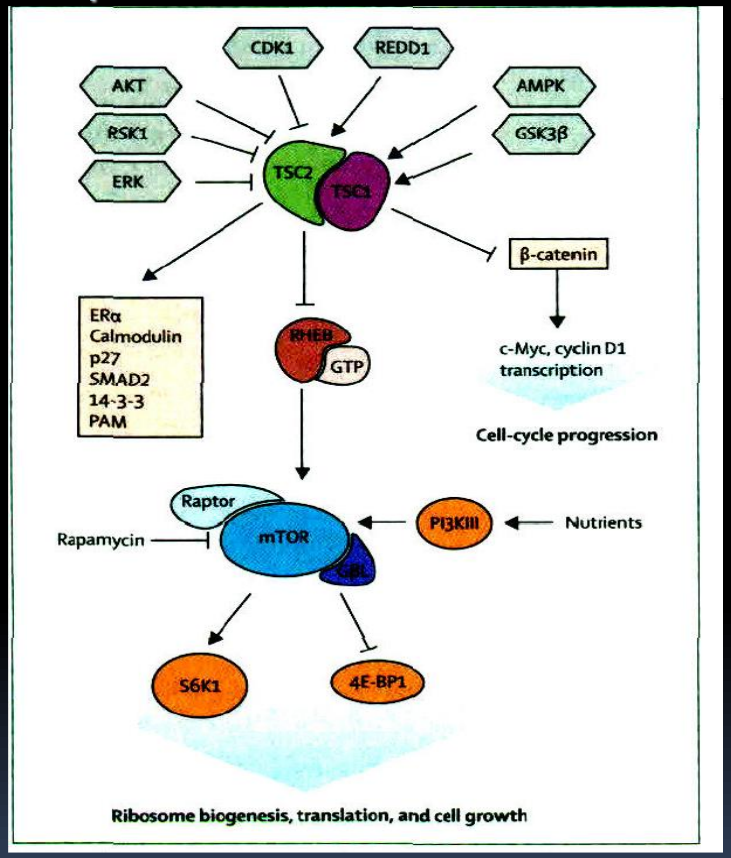


Figure 2: **The hamartin–tuberin complex: central regulator of cell-signalling pathways**
After growth-factor stimulation, the hamartin–tuberin complex is phosphorylated and its GTPase-activating protein activity is decreased, whereas in response to stimuli such as hypoxia or low energy it is phosphorylated and its GTPase-activating protein activity increased. The complex deactivates RHEB by causing GTP to be cleaved from it. Activated RHEB stimulates mTOR, which has a crucial role in the translation of proteins such as c-Myc or ornithine decarboxylase, and participates in cell-cycle control. mTOR binds to raptor and GβL to exert its effect, which is mediated by S6K1 and 4E-BP1, proteins that participate in ribosome biogenesis and translation initiation, respectively. Nutrients might boost translation through PI3KIII, which phosphorylates mTOR. TSC1 and TSC2 interact also with other proteins, such as ERα, calmodulin, p27, SMAD2, 14-3-3 proteins, and PAM. 4E-BP1=eukaryotic translation initiation factor 4E binding protein 1. AKT=protein kinase B. AMPK=AMP-activated protein kinase. CDK1=cyclin-dependent kinase 1. ERK=extracellular signal-regulated protein kinase. GβL=G protein β-subunit like. GSK3β=glycogen synthase kinase 3β. PAM=protein associated with Myc. PI3KIII= PtdIns 3-kinase. REDD1=regulated in development and DNA damage responses. RHEB=Ras homologue enriched in brain. RSK1=ribosomal S6 kinase 1. S6K1=kinase that activates ribosomal subunit S6.

New developments : mTOR pathway

- The delineation of the TSC signalling pathway suggest strategies for targeted therapy, including mTOR inhibition
- mTOR inhibition can prevent the dev of epilepsy in a mouse model with conditional deactivation of TSC1 gene
- A retrospective clinical study confirmed usefulness of rapamycin in CWE and TSC
- Several studies now
- We participate in a multicentre international study of Everolimus In RE and TSC
  - Sabassov, 2005. Curatolo 2008, Zeng,2009. Canpolat 2014. Kruger et al, Annals of Neurol 2013.Krueger et al, Eur J of Paed Neurol 2018.

Mammalian Target of Rapamycin Pathway (mTOR) in epilepsy syndromes

- Tuberous sclerosis Complex – one of the commonest causes of IS
- Epilepsy also associated with other genes in this pathway- hemimegelencephaly, PTEN mutations, STRAD alpha gene,
- Dysregulation of mTOR pathways can occur in other epilepsies – CD with balloon cells may have loss of heterozygosity and polymorphisms in the TSC1 gene.
- mTOR may be involved in a variety of insults associated with IS and epilepsy– trauma, HIE, PAIS, Szs
- mTOR inhibitors may have anti-sz and anti-epileptogenic effects in a number of situations, may not have in some.
- GATOR pathway…
- Galaopoulou et al, Epilepsia 2012. Huang et al, Neurobiol 2010

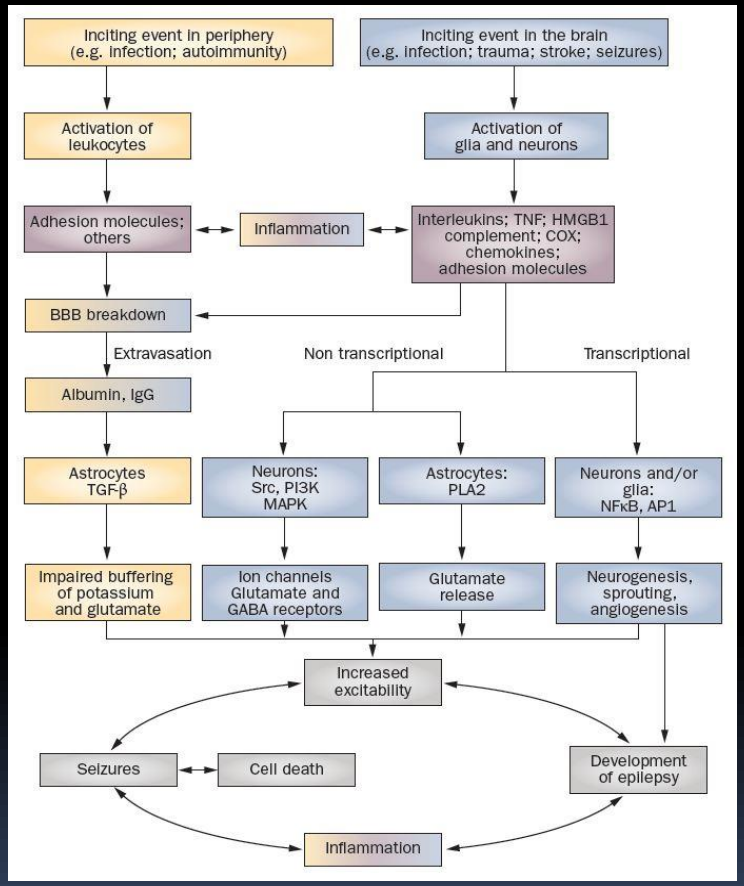
Role of Brain Inflammation in Epilepsy

- Inflammation: cause or consequence of epilepsy
- Clinical evidence that steroids displayed anticonvulsant activity in some children with difficult epilepsy - suggesting a potential role for immune modulation in epilepsy
- Febrile szs coincide with and ? caused by rise in pro-inflammatory agents
- Rasmussen's encephalitis, limbic encephalitis, szs with autoimmune disorders (5 fold increase) suggest inflammatory and immunological mechanisms have a role in epilepsy
- Vezzani et al, Nature Reviews.2011, Legido and Katsetos, Sem in Ped Neurol. 2014, Ruegg and Panzer, Neurology.2014, Koh, J of Child Neurol.2018

Innate and Adaptive immunity implicated in Epilepsy

- Brain- traditionally considered to be "**immuno-priviliged**"
  - presence of the blood brain barrier, lack of lymphatic system and ltd trafficking of peripheral immune cells
- **Innate immunity** in the brain:
  - represents a non specific immediate host response against invading pathogens/noxious stimuli.
  - It is thought to be activated and mediated by microglia, , astrocytes, neurons, endothelial cells of the BBB, leukocytes, Toll Like Receptors (TLRs)…
- **Adaptive immunity:**
  - is activated in response to innate immunity, enables the brain to recognise and remember specific non self antigens and mount a humoral and cell mediated inflammatory response.
- **Dysregulation of adaptive immunity may lead to loss of tolerance to self antigens and result in autoimmunity.**

Vezzanie et al . Nature Reviews 2011



Immunological and inflammatory mechanisms and epilepsy

- Epilepsies of various aetiologies (eg TLE, Cortical dysplasias) not classically linked to immunological dysfunction can be associated with inflammation
- Brain inflammation may contribute to the start of szs and perpetuation of the epileptogenic process – Szs can cause inflammation, inflammation affects seizure severity and recurrence and inflammation may cause cell loss
- Inflammation can be neuroprotective , in epilepsy the balance may be skewed.

Autoimmune epilepsy in children

- **Adaptive** immune system activated
- Acute/subacute onset of szs, neuropsychiatric manifestations, encephalopathy, EEG changes, inflammation of CNS on CSF analysis and MRI
- Association of pathogenic neuronal antibodies such as NMDAR, VGKCC , glycine receptor, GABA Type A and B receptors, GAD antibodies.
- These antibodies support but are not essential for diagnosis
- Suleiman et al. Epilepsia 2013. Suleiman &Dale. Developmental Medicine and Child Neurology 2014

Immune mediated Epilepsy Syndromes

- Rasmussen's
- FIRES
- NMDA -R mediated encephalitis
- Treatment – with Steroids, IVIG, monoclonal antibodies

Cation Chloride Cotransporters:CCCs

- Various epileptic insults and injuries may down-regulate the KCC2 and upregulate the NKC1
- Bumetanide inhibitor of NKCC1
- ? How useful.

- Kaley and Staley Neurosurg Focus 2008. Singh et al. Ann Neurol 2009. Kaley et al JCN 2009. Nardou et al Brain 2011. Puskarjov Epilepsia 2014

Dravet Syndrome

- Sodium Valproate, Topiramate, Clobazam
- Stiripentol – syndrome specific
  - In combination with VPA and Clobazam has been shown to be effective in a randomised placebo controlled trial
  - Cytochrome p450 inhibition, enhances gabanergic neuroinhibition
- Drugs that may worsen the EE:
  - CBZ, gabapentin, OCZ, LTG, PHT, Tiagabine, Vigabatrin
- Chiron 2000. Guilichini 2006. Grosenburg 2013.

Genes and epilepsy

- With the advent of next generation sequencing rapid advances in genetic cause of epilepsies (Mastrangelo, 2015)

- Targeted therapies emerging (Milligan, 2014, Pearson 2014)
  - eg Quinidine for KCNT1 mutations
  - Memantine for GRIN 2A mutations

Stem Cell therapy
Gene Therapy
for Epilepsy

- ? Therapeutic Reality

- Intraparenchymal approach: need invasive brain surgery for delivery
- ? Non invasive approach an option: intravascular injection a possibility

- Sorensen et al, Epilepsia, 2013

Gene Therapy in the Nervous System

- Involves transfer and expression of genes into the brain, most commonly to the neurons in the brain, using viral vectors.
- The viral vectors appear to promote long term gene expression, without neurotoxicity, have the ability to transduce non-dividing cells, may be amenable to posttranscriptional control.
- Targets could be
  - Dampening of hyperexcitability by transduction of endogenous cells and expression of inhibitory modulators
  - Transduction of endogenous cells that facilitate inhibitory firing or expression of opsins that reduce firing in excitatory pathways.
  - Promote survival of affected neurons and repair of partially damaged circuits

Gene Therapy Targets for Epilepsy

- Galanin
  - suppresses excitatory glutamatergic transmission
  - ?prevent epileptogenesis and inhibit focal seizures, ? potential adverse effects

- Neuropeptide Y - NPY and NPY (Y2)receptors
  - controls neuronal excitability by decreasing glutamate release, may delay epileptogenesis
  - Most attractive gene therapy approach

Gene Therapy Targets for Epilepsy

- Neurotrophic Factors – GDNF, BDNF,..
  - Important as survival factors for developing neurons, support existing adult neurons, and regulate synaptic plasticity.
  - ?endogenous protective mechanism against neuronal damage due to excitotoxicity, preventing epileptogenesis, but also anti seizure effect

- Adenosine – activation of A1 receptors, knockdown of adenosine kinase (ADK)
  - ? results in seizure arrest and postictal refractoriness, inhibits excitatory glutaminergic transmission
  - ADK knockdown in astrocytes is a promising AED target.

Stem Cell Based Therapy in Epilepsy

- Neurons and glial cells can be generated, from embryonic, mesenchymal, neural, induced pluripotential and induced neuronal stem cells.

- May be beneficial by
  - Cell replacement to repair neural networks
  - Trophic support to promote endogenous repair and survival
  - Genetically modified stem cells (GABA releasing, Adenosine releasing) release of therapeutic compounds – neuroinhibitory or neuroexcitatory.

Optogenetic: Emerging Strategy for Epilepsy

- Manipulation of brain activity with light
  - the basis of optogenetics is the presence of light sensitive proteins in the brain
  - light sensitive proteins are genetically encoded, therefore they can be introduced into the CNS, in anatomically or functionally defined groups of cells using viral vectors and population specific promoters.
  - Thus endogenous GABAnergic neurons can be activated or excitatory neurons can be silenced
  - At present, light driven ion pumps or proton pumps (NpHR, BR), when activated can hyperpolarise neurons and if this happens in excitatory neurons the overall excitability of the circuit is dampened.

Ketogenic Diet

- First line treatment for kids with GLUT-1defects, PDH deficiency, as it provides an alternate source of fuel
- Alternative treatment to AEDs in TREC and the EEs
- Particularly useful in MAE, LGS, Dravet syndrome, EEs with generalised seizures, especially with frequent myoclonic seizures
- McTague 2013, Vigevano 2013

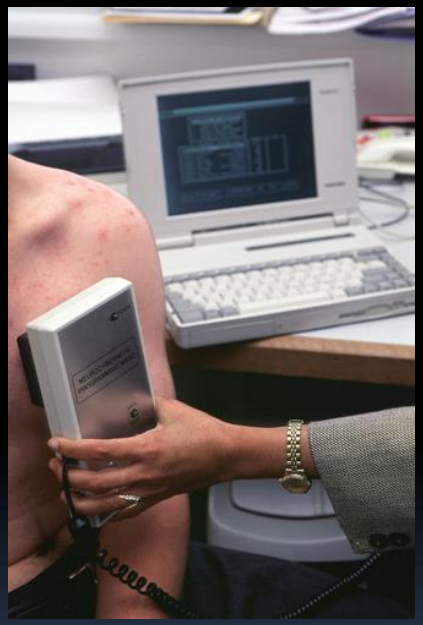
Surgery

- Lobar Resections
- Lesionectomies
- Hemispherectomy
- Corpus Callosotomy

Edelvik, 2013, Nagarajan 2015.

Vagal Nerve Stimulation

Nagarajan et al, 2002, 2003.



New Modalities

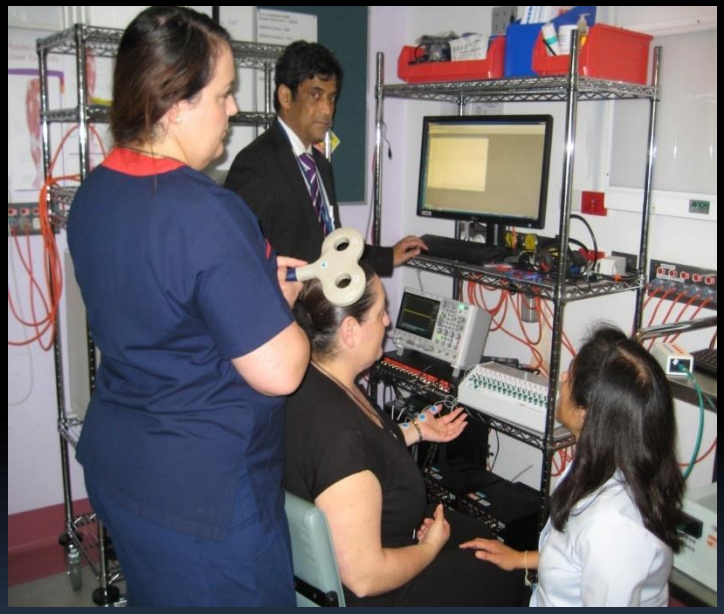
- Non Invasive Brain Stimulation
- Responsive Brain Stimulation
- Deep Brain Stimulation

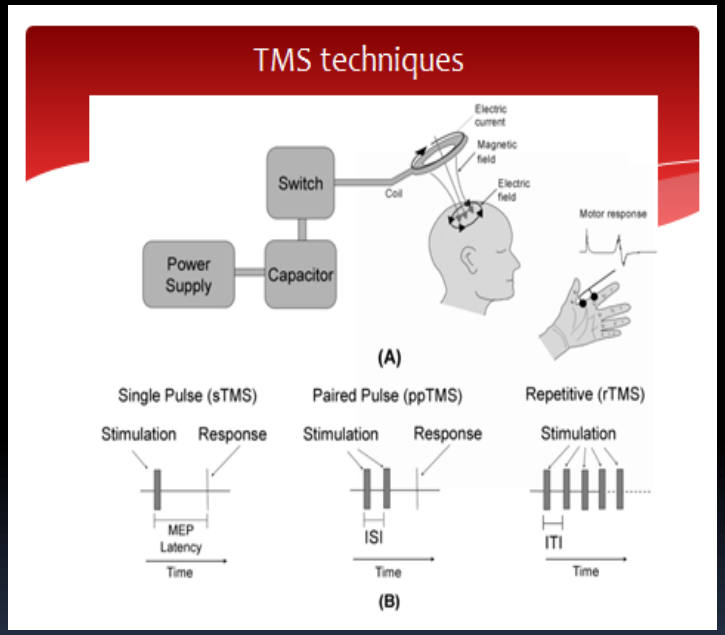
Non Brain Invasive Brain Stimulation in Epilepsy

- TMS
  - Transcranial Magnetic stimulation
- tDCS
  - Transcranial Direct Current Stimulation
  - Ghosh & Nagarajan, JICNA,2016.

Applications of TMS/ tDCS in epilepsy

- Monitor effectiveness of AEDs and other treatments
- Predict seizures
  - Changes in cortical excitability (increase upto 24 hours before and reduce post-ictal)
- Interventional studies
- rTMS and tDCS to modulate cortical excitability




TMS techniques
Electric current
Magnetic field
Electric field
Switch
Coil
Power Supply
Capacitor
Motor response
(A)
Single Pulse (sTMS)
Paired Pulse (ppTMS)
Repetitive (rTMS)
Stimulation
Response
Stimulation
Response
Stimulation
MEP Latency
ISI
ITI
Time
Time
Time
(B)

TMS in children

- Normal children
  - Development of normal motor pathways
- Neurological disorders
- Reorganization after brain injury
  - Cerebral palsy
- Diagnostic studies
  - MS, transverse myelitis, cerebellar ataxia
- Monitoring corticospinal function
- Neuropsychiatric abnormalities: ADHD, TS

TMS in childhood epilepsy

- Fewer studies
- Reduced inhibition in children with focal refractory epilepsy
  - Reduced SICI and LICI (Inghilleri et al. 1998; Werhahn et al. 2000; Shimizu et al. 2001; Badawy et al. 2013)
- Few interventional studies (few children in each study)
  - rTMS reduces frequency of epileptiform discharges, no effect on seizures in most children (Fregni et al. 2005)
  - tDCS reduces frequency of epileptiform discharges, small reduction in frequency of seizures in some children (Auvichayapat et al. 2013)

Transcranial Direct Current stimulation: tDCS

- Direct electric current applied to scalp (1-2mA)
- Excitatory effect under anode
- Inhibitory effect under cathode

- Lasts minutes (longer?) after stimulus applied
- Causes neuronal membrane de/ hyper-polarization and changes spontaneous firing rates

- Effects blocked by Na+ channel blockers and NMDA antagonists

- tDCS causes widespread changes in blood flow and cortical excitability (PET, fMRI, MRI spectroscopy)

tDCS: Safe and painless technique

- Role in studying brain function and treatment of neurology and psychiaty being explored
  - 1-2mA for 20 minutes for 5-10 days
- Clinical trials in depression, chronic pain, stroke
- Cathodal tDCS increases sz threshold in animals
- Clinical trials with rTMS and tDCS in refractory epilepsy

Our Research projects

- TMS study
  - Cortical excitability in benign focal epilepsies of childhood – BFEC, BOEC
  - evaluate the role of TMS in predicting response to therapy and in prognostication

- tDCS study
  - Interventional study exploring efficacy and tolerability of tDCS in refractory childhood epilepsy.

Targeted Therapies and New Options in Epilepsy

- New Horizons
- Optimistic
- Hope not just hype!
- THANK YOU