

**Management medical refractory cases with newest generation AEDs**

What can be expected ?

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**Outline**

- Overview medical management of refractory epilepsy
- Cases: Refractory seizures with New AEDs
  - LCM: Dr. Charchrin
  - Perampanel: Dr. Yotin

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**Medical management of refractory epilepsy**

- The ultimate treatment goal in epilepsy therapy is always **freedom from seizures** with as **few treatment adverse effects** as possible
- If seizures persist with the first monotherapy, **alternative monotherapy** with another antiepileptic drug (AED) should be considered
- Continuing seizures should lead to a **reevaluation of differential diagnosis and adherence**

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**Medical management of refractory epilepsy**

- **Epilepsy surgery** as alternative therapy may be suitable in selected cases
- If the diagnosis of epilepsy is established and epilepsy surgery is not appropriate, AED treatment should be optimized
- **Evidence for how to proceed is lacking**

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**Medical management of refractory epilepsy**

- Concepts such as **rational polytherapy** have been advocated but remain speculative concerning better efficacy based on **use of AEDs with differing modes of action**
- A variety of new AEDs including
  - Rufinamide
  - Lacosamide
  - Perampanel
  - Retigabine

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**Seizure Exacerbation**

- When adding a second or third AED, it is important to **avoid adding an AED that may worsen or provoke seizures** i.e.
  - CBZ (carbamazepine), OXC (oxcarbazepine), PHT (phenytoin), VGB (vigabatrin), and TGB (tiagabine) may **worsen myoclonus and absences**
  - GBP (gabapentin) - **myoclonus**
  - LTG (lamotrigine) - **myoclonus**
  - Benzodiazepines - **tonic seizures**

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**Seizure Exacerbation**

- Seizure exacerbation problem encountered mainly in **GABAergic AEDs** (TGB, GBP, and VGB) and **sodium channel blocking AEDs** (PHT, CBZ, and LTG)
- **Natural fluctuation of seizures** over the course of a year: factor that must be taken into account when deciding if seizure exacerbation really occurred
- Need to understand changes in these variables might be due to new AED or a **pharmacodynamic interaction** between new AED and other AEDs

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**Rational Polytherapy**

- Adding new AED to existing therapy one should **choose an AED with different mechanism of action** other than drug or drugs already being given
- Adding a sodium channel blocker i.e.
  - **LCM to another sodium channel blocker such as CBZ might achieve seizure control**, but dizziness could be higher in patients on CBZ- LCM combination than on non-sodium channel blocking agent + LCM
- **Many of AEDs have other mechanisms of action** as well as major mechanism. These other activities contribute to antiepileptic function
  - LEV mainly affect the SV2a, but has even calcium-modulating properties and GABAergic properties
  - CBZ, although sodium channel blocker, has other mechanisms of action as well

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**AED Synergism**

- Adding another AED to one with different mechanism of action will enhance efficacy greater than assumed efficacy addition of both
- However, only a few studies have implied that the addition of one drug to existing AED increases the efficacy more than the expected i.e.
  - LTG additional to the VPA

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Perampanel in Refractory seizures

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| Case | Sz type         | Dx             | Surgery                              | Etiology              | Med               | Perampanel (mg/day) | Response                       | Adverse drug reaction |
|------|-----------------|----------------|--------------------------------------|-----------------------|-------------------|---------------------|--------------------------------|-----------------------|
| F 31 | SPS, CPS, 2GTCS | TLE            | ATL Lt                               | Lt: hippo atrophy     | VPA, LVT, LTG     | 12                  | 50% Sz reduction               | No                    |
| F 44 | SPS, CPS, 2GTCS | Focal epilepsy | No                                   | Lt. MTS               | CBZ, LTG, ZNS     | 12                  | 50% Sz reduction               | No                    |
| M 48 | CPS, 2GTCS      | TLE            | No                                   |                       | LVT, CBZ, TPM     | 12                  | 50% Sz reduction               | No                    |
| M 25 | CPS             | TLE            | No                                   | Bilat MTS             | TPM               | 10                  | Not improved                   | Dizziness             |
| F 32 | CPS             | TLE            | No                                   | Cystic lesion Lt Temp | LVT, VPA, PGB     | 6                   | 50% Sz reduction, but loss FUJ | Wt gain, dizziness    |
| M 13 | GT, 2 GTCS      | PLE            | Corpus callosotomy, two corticectomy | Cortical dysplasia    | PB, LTG, VPA, CLZ | 6                   | Not improved                   | No                    |

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**CASE II**

- F 31 yrs old
- Hx 1 st Sz 15 year old, Sz type SPS, CPS, 2 GTCS
- TLE with left hippocampal atrophy
- Hx ATL Lt Oct 2007, patho: gliosis with neuronal loss
- Sz 1-3 per months, Med: LTV (1250), LTG (200), VPA (2000)

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### CASE II

- Started Perampanel 2013
  - 2 --- 4--- 8 --- Currently 12 mg per day
  - Sz 1 per month, patient feel improvement when using Perampanel
- No any ADR

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### Refractory case

- Master 13 years old, Intellectual disability with Epilepsy
- Hx of 1<sup>st</sup> seizure 8 months old, Hx Prematurity birth 7 months old BW 1645 Kg, patient had disability unable to walk, motor all gr IV+
- Sz type:
  - Tonic seizure, lasting a few seconds, usually come in cluster 4-5 cluster per day, ~ 10 times of Sz / cluster,
  - 2 GTCS

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### case

- Had corpus callosotomy in 2009, Epilepsy surgery with subdural grid Lt PO in 2011, Had 2<sup>nd</sup> Operation Left PO region in 2012, Patho CD
- Previous investigation
  - Ictal EEG epileptiform D/C both CH, predominantly Rt. Temporo-parieto-occipital region
  - MRI brain dilated ventricle Lt > Rt, abnormal gyrus bilateral parieto-occipital lobes
  - Ictal SPECT Inc rCBF Rt. Parieto-occipital region

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### case

- Post operation
  - Medication: PB: ZNS, VPA, LTG: Sz frequency 3-4 cluster per day
  - Later on Sz frequency 10-30 time per day
  - Current medication: PB, LTG, VPA, CLZ
  - Had been tried Lacosamide: Sz unchanged
- March 2015: Sz increased 50 Sz per day
- Medication: PB, LTG, VPA, CLZ

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### case

- Then, Perampanel was started 2 mg per day
- Gradually titrated up from 2 to 4 to 6 mg every two weeks nearly three months
- Last visited late June 2015, Patient on Perampanel 6 mg per day, Sz still unchanged 1-3 cluster per day, around 10-70 Sz per day

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### Comment

- In treating epilepsy, must weigh many factors for [choosing appropriate AED](#) and also when to go [surgical evaluation and other therapeutic methodologies](#) when patient became refractory to appropriate two or three AEDs
- Physician have to learn about all AEDs available, both new and old, to tailor treatment according to requirements of each patient
- Not easy task, need to
  - Understand [mechanisms of action](#)
  - [Metabolism and dosing, interactions, potential side effects](#)
  - How to deal with them, as well as appropriate seizure types for each drug, and [how to combine the different drugs](#)

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