

# **Old vs New Medicines in Epilepsy**

**- Therapeutic Algorithms -  
Peter Wolf, Denmark**

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# **Old vs. new or complexity?**

**When we had fewer drugs, our algorithms were easier.**

**Their increased complexity is a direct function of  $> N$  possibilities.**

**Opposing old and new drugs may to a certain extent be a misdirected attempt to reduce a complexity which in fact should be welcomed because -**

**the more different drugs we have, the better the chances that one will be found which has the desired effect.**

# **Experience vs. evidence**

**In former times, therapeutic decisions were founded on experience - which is a mythological category based on mere subjectivity - perhaps.**

**Now we live under the rule of evidence-based therapy - which creates its own myths - e.g. the myth of objectivity.**

# **Subjectivity in evidence-based AED therapy**

- **Rates of reduction in seizure frequency from regulatory studies understood as indicators of therapeutic power.**
- **Side effect profiles deducted from regulatory studies.**
- **“Add-on” considered different from combination therapy.**

# **Are there evidence-based algorithms in AED therapy?**

- **Problems of comparative studies of AEDs as first therapies:**
  - many light epilepsies → no differences
  - syndrome classification at onset?
  - no long-term follow-up
- **Comparative studies of 2nd, 3rd AED after failure of 1st drug missing.**

# The crucial question

**If we have a patient with epilepsy syndrome X who keeps getting seizures with a well-selected AED A:**

**what are his/her % chances to obtain full seizure control with AEDs B,C,D and E?**

**With this knowledge, we could then make a rational selection, considering also these drugs' side effect profiles.**

# The situation

**As we are far from knowing these answers, even for a single of the more common syndromes:**

**we need to make optimal use of the modest evidence which is there, and combine it with the best-established experience available.**

# **The 1st maxim of epilepsy therapy**

**The aim of therapy is full seizure control,  
because this is the most important  
precondition for worthwhile  
improvements of the patients' life  
quality,**

**and the only sure prevention of secondary  
complications -  
including SUDEP.**

**This maxim must guide our algorithms.**

**The 2nd maxim of epilepsy therapy**  
**The therapy must not do more harm  
than good.**

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**Two conclusions from these two maxims:**

- 1) Of several therapy alternatives, the least risky must be taken, keeping in mind that no effective treatment is without any risk;**
- 2) If full control is not achieved with a well-chosen drug, an alternative drug's potential risk, or its age are no good arguments against using it.**

# Algorithms for focal epilepsies

- **For a first choice, the most frequently recommended drugs are Carbamazepine (CBZ) and Valproate (VPA). The evidence for their equality is not based on difficult epilepsies, and only CBZ is considered standard prerequisite before a decision for surgery.**
- **Some hold that Oxcarbazepine (OXZ) should now be preferred for CBZ. The arguments used for that are not based on therapeutic success, and the evidence for better tolerability is meagre. Elder people tolerate OXZ less.**
- **If CBZ fails, there is at present no data giving evidence as to the most promising next choice.**

# **Focal epilepsies: 2nd line choices**

- **Of the new drugs, both Lamotrigine (LTG), Topiramate (TPM) and Levetiracetam (LEV) can be considered good candidates.**
- **A failure of CBZ does not predict a failure of OXC but it seems more rational first to try another drug which is chemically unrelated.**
- **Even if monotherapy is the gold standard, a combination of LTG and VPA should precede the use of old drugs because it has a supra-additive therapeutic interaction.**
- **Of the old drugs, Phenytoin (DPH) and Phenobarbital (PB) are classical and, even if there are some problems attached, their use is much preferable to therapeutic nihilism.**
- **Mesuximide (MS) is one of the rare old drugs where a controlled study showed effect in focal seizures.**

# **Focal epilepsies: the surgical option**

- **Patients with focal epilepsies are the group where surgery can and should be considered.**
- **The best results are in mesio-temporal lobe epilepsy with hippocampal sclerosis (MTLHS), and in cortical epilepsies with a morphological finding.**
- **One controlled study has shown that, in patients with MTLHS where 2 or more AEDs have failed, resective surgery (with ongoing drug treatment) is more efficient than the use of still more drugs.**
- **Surgery should be considered when 2 drugs for focal epilepsy have failed, in MTLHS and cortical epilepsies with lesions on MRI.**
- **Precondition: the resistant seizures are disabling.**

# **Idiopathic localisation-related epilepsies**

- **Best known: benign childhood epilepsy with centro-temporal spikes (“rolandic epilepsy”):**
- **AED not always necessary.**
- **If yes: Sulthiam first choice.**
- **2nd line not well established.**

# Algorithms for generalised epilepsies: absences

- The traditional drugs are VPA and ethosuximide (ES) which can be used alone or together. If the patient has also GTC seizures, ES needs to be supplemented by a drug against these. VPA works for both.
- LTG is increasingly replacing VPA especially in young women (weight; teratogenic risk; ovarian cysts?). ES should not be forgotten.
- Place of TPM; LEV?

## **Algorithms for generalised epilepsies: juvenile myoclonic epilepsy (JME)**

- **VPA considered drug of 1st choice because active against both myoclonic seizures, the frequent GTC sz, the occasional absences, and the frequent photosensitivity.**
- **But: same caveats of side effects as before.**
- **Clonazepam (CLZ) useful for myoclonic but not for GTC seizures, and high risk of withdrawal sz.**
- **LTG perhaps less effective against myoclonic and GTC seizures.**
- **Traditional drug: Primidone (PRM) / Phenobarbital.**
- **Contraindication for CBZ, DPH.**
- **Searchlight on TPM, LEV.**

# **Algorithms for generalised epilepsies: EGMA**

- **VPA now considered drug of 1st choice, but same caveats as before.**
- **No good evidence for 2nd line. Action of LTG, TPM, LEV against GTC sz not well established -**
- **maybe not better than CBZ or DPH.**
- **Traditional 1st choice: PB / PRM.**
- **Last resort: Bromide.**

## **A final question**

**Should treatment with an old AED, when the patient has no seizures, be changed to a new one because this would decrease the risk of side effects?**

**The risk of side effects must be weighted against the risk of seizure relapse.**

**The answer is: NO,  
don't change a winning team!**