

Things that You Do Not Want to Miss

Subtle & Confusing Manifestations of Epilepsy

Epilepsy (Subtle/Confusing Manifestations)

1. Absence vs preoccupation
2. Complex partial vs confusion arousal
3. Frontal lobe seizure vs RESM sleep behaviour
4. Complex partial seizure vs psychosis
5. Atonic seizure vs syncope/fainting episode

Absence

vs

Preoccupation



Complex Partial

vs

Confusion Arousal



Frontal Lobe Seizure

vs

RESM Sleep Behaviour



Complex Partial

vs

Psychosis



Atonic Seizure

vs

Syncope/fainting episodes



Absence

vs

Complex Partial



Non-convulsive Status

Non-convulsive Status

- A form of continuous partial seizure activity, usually with focus from frontal or temporal lobe.
- Presented with alert but dull mental state, with variable memory loss, disorientation and mood changes on a middle-aged or elderly with no past history of seizure.
- EEG – continuous or nearly continuous 1 to 2.5 Hz generalized spike-wave activity.
- Possible aetiology:
 - HHNK, electrolyte imbalance, drug toxicity, focal cerebral lesion

Epilepsy

Update on Pharmacotherapy

AEDs in U.S.

- 1910's: Phenobarbital
- 1930's: Methobarbital, Phenytoin
- 1940's: Trimethadione, Mephenytoin, Paramethadione
- 1950's: Phenacemide, Metharbital, Phensuximide, Primidone
 - Methsuximide, Ethotoin
- 1960's: Ethosuximide, Diazepam
- 1970's: Carbamazepine, Valproate
- 1990's: Felbamate, Gabapentin, Lamotrigine, Topiramate
 - Tiagabine
- 2000's: Zonisamide, Levetiracetam, Oxcarbazepine
- Pending: Remacemide, Pregabalin, Rufinamide

AAN's Class of Evidence

Class I:	A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.
Class II:	A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most (>80%) patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

AAN's Class of Evidence

Class III:	A selected, referral-clinic-based sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.
Class IV:	Expert opinion, case reports or any study not meeting criteria for class I to III.

AAN's Recommendation Levels

Level A =	Established as useful/predictive or not useful/predictive for the given condition in the specified population.
Level B =	Probably useful/predictive or not useful/predictive for the given condition in the specified population.
Level C =	Possibly useful/predictive or not useful/predictive for the given condition in the specified population.
Level U =	Data inadequate or conflicting. Given current knowledge, test, predictor is unproven.

Update on Anti-epileptic Pharmacotherapy “Newly Diagnosed Epilepsy”

Questions of Interests

- How does the efficacy and tolerability of the new AEDs compare with that of older AEDs in patients with *newly diagnosed epilepsy*?
- Are the new AEDs effective in *adults or children with newly diagnosed primary or secondary generalized epilepsy*?

New AEDs (Efficacy & Tolerability)(1)

Efficacy in newly diagnosed patients:

- Gabapentin is effective in the treatment of *newly diagnosed partial epilepsy*.
- Lamotrigine, topiramate, and oxcarbazepine are effective in a mixed population of *newly diagnosed partial and generalized tonic-clonic seizures*. There is insufficient data to make a recommendation for the syndromes individually.
- At present, there is insufficient evidence to determine effectiveness in newly diagnosed patients for tiagabine, zonisamide, or levetiracetam.

New AEDs (Efficacy & Tolerability)(2)

Comparison to standard AEDs:

- Oxcarbazepine is equivalent to carbamazepine and phenytoin in efficacy, but superior in dose-related tolerability, at individually determined doses.
- Oxcarbazepine is equivalent in efficacy and tolerability to valproic acid.
- Topiramate at doses of 100 and 200 mg/day was equivalent in efficacy and safety to 600 mg fixed dose carbamazepine and 1250 mg/day valproic acid, both in children aged 6 years and older and adults.
- Lamotrigine is equivalent in efficacy to carbamazepine and phenytoin and superior in tolerability to carbamazepine, both in adults and elderly individuals.

New AEDs (Efficacy & Tolerability)(3)

Comparison to standard AEDs:

- Topiramate at 100mg and 200 mg are equivalent in efficacy and safety to 600 mg of fixed-dose, immediate-release carbamazepine administered in a BID regimen for partial seizures and to 1250 mg of fixed-dose valproic acid for idiopathic generalized seizures.
- Gabapentin is effective in monotherapy at 900 and 1800 mg and is equivalent in efficacy to a 600 mg fixed dose of carbamazepine. Nine hundred milligrams of gabapentin is better tolerated than 600 mg fixed-dose, short-acting carbamazepine administered in a BID schedule.

Recommendation

- Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice of AED will depend on individual patient characteristics. **(Level A)**

Questions of Interests

- How does the efficacy and tolerability of the new AEDs compare with that of older AEDs in patients with *newly diagnosed epilepsy*?
- Are the new AEDs effective in *adults or children with newly diagnosed primary or secondary generalized epilepsy*?

New AED Efficacy (Generalized Seizure – Primary & Secondary)(1)

- Lamotrigine is effective in the treatment of *children with newly diagnosed absence seizures*.
- At present, there is insufficient evidence to determine effectiveness in newly diagnosed primary or secondary generalized epilepsy for topiramate, oxcarbazepine, tiagabine, zonisamide, or levetiracetam.

Conclusions

- Lamotrigine is effective in children with *newly diagnosed absence seizures*.

Recommendation

- Lamotrigine can be included in the options for children with *newly diagnosed absence seizures* **(Level B)**.

Summary of AAN Evidence-Based Guidelines (level A or B)(1)

AED	Newly Diagnosed Monotherapy Partial/mixed	Newly Diagnosed Absence
Gabapentin	Yes*	No
Lamotrigine	Yes*	Yes*
Topiramate	Yes*	No
Tiagabine	No	No
*Not FDA approved for this indication		

Summary of AAN Evidence-Based Guidelines (level A or B)(2)

AED	Newly Diagnosed Monotherapy Partial/mixed	Newly Diagnosed Absence
Oxcarbazepine	Yes	No
Levetiracetam	No	No
Zonisamide	No	No
*Not FDA approved for this indication		

New AEDs (Adverse Events)(1)

AED	Serious Adverse Events	Nonserious Adverse Events
Gabapentin	None	BWeight ↑, peripheral edema, behav changes*
Lamotrigine	Rash, including Stevens Johnson and toxic epidermal necrolysis (↑ for children, also more common with concomitant valproate use and ↓with slow titration); hypersensitivity rxns, i.e. risk of hepatic and renal failure, DIC, and arthritis	Tics* and insomnia

New AEDs (Adverse Events)(2)

AED	Serious Adverse Events	Nonserious Adverse Events
Levetiracetam	None	Irritability/behavior change
Oxcarbazepine	Hyponatremia (more common in elderly), rash	None
Tiagabine	Stupor or spike wave stupor	Weakness
Topiramate	Nephrolithiasis, open angle glaucoma, hypohidrosis (predominantly children)	Metabolic acidosis, weight loss, language dysfunction
Zonisamide	Rash, renal calculi, hypohidrosis (predominantly children)	Irritability, photosensitivity, weight loss

Update on Anti-epileptic Pharmacotherapy

“Refractory Seizure”

Questions of Interests

1. Are the new AEDs effective in *refractory partial epilepsy as adjunctive therapy*?
2. Are the new AEDs effective in *refractory partial epilepsy as monotherapy* ?
3. Are the new AEDs effective in *refractory idiopathic generalized epilepsy*?
4. Are the new AEDs effective in *refractory partial epilepsy as adjunctive therapy in children*?
 - Are the new AEDs effective for *refractory idiopathic generalized epilepsy in children*?
 - Are the new AEDs effective for *Lennox-Gastaut syndrome in children and/or adults*?
 - What is the risk of teratogenicity with the new AEDs compared to the old AEDs?

Refractory Seizure

- There is no unifying definition of refractory epilepsy.
- Often, patients are referred to as refractory, or treatment resistant when they have “failed” 3 or more AEDs.

Summary of Findings

Effective in ↓ seizure frequency as adjunctive therapy in patients with *refractory partial seizures*:

- **Gabapentin**, (600-1800 mg)
- **Lamotrigine**, (300 mg-500 mg in enzyme-induced patients, and 150 mg/day in patients receiving enzyme inducers and valproic acid)
- **Levetiracetam**, (1000-3000 mg)
- **Oxcarbazepine**, (600-2400 mg)
- **Tiagabine**, (16-56 mg)
- **Topiramate**, (300-1000 mg)
- **Zonisamide**, (100-400 mg)

Summary of Findings

- **Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine and zonisamide** are more effective at higher doses.
- **Levetiracetam**, the evidence for a dose-response for is less clear, but more patients were seizure free at 3000 mg than 1000 mg.
- Side effects and dropouts due to side effects also increase in a dose-dependent manner for all these drugs.

Summary of Findings

- **Oxcarbazepine**, when administered at the titration rate used in the add-on trial (which is the rate recommended in the package insert) has a particularly marked dose-related toxicity. At the highest dose used, 67% of patients dropped out, most in the first few weeks of therapy.
- **Gabapentin** and **topiramate**, slower initiation/titration reduces side effects.
- This may be true for the other AEDs as well, but no class I or II evidence is available to support this.

Conclusion

- All of the drugs have demonstrated efficacy as add-on therapy in patients with *refractory partial epilepsy*.
- Even though the methodology was similar for all studies, it is not possible to determine relative efficacy from comparison of outcomes, because populations differed (as evidenced by differing placebo responder rates), and some drugs were not used in maximum doses, whereas others appear to have been administered above ideal dose, as evidenced by high dropout and side effect rates.

Conclusion

- For essentially all drugs, efficacy as well as side effects increased with increasing doses.
- In all cases where two different titration rates were compared, the slower titration was better tolerated. Therefore, it would seem advisable to start low and go slow, using increasing doses until side effects occur (in other words, push to maximum tolerated dose).

Recommendation

- It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam and zonisamide as add-on therapy in patients with refractory epilepsy (**Level A**).

Questions of Interests

1. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy*?
2. Are the new AEDs effective in *refractory partial epilepsy* as *monotherapy* ?
3. Are the new AEDs effective in *refractory idiopathic generalized epilepsy*?
4. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy* in *children*?
 - Are the new AEDs effective for *refractory idiopathic generalized epilepsy* in *children*?
 - Are the new AEDs effective for *Lennox-Gastaut syndrome* in *children* and/or *adults*?
 - What is the risk of teratogenicity with the new AEDs compared to the old AEDs?

Summary of Findings

- **Lamotrigine**, 500 mg/day
 - Superior to 1000 mg/day of valproate (acting as a “pseudoplacebo”).
 - Is effective in *monotherapy* for *refractory partial epilepsy*.
- **Oxcarbazepine**, 2400 mg/day
 - Superior to 300 mg/day, and is therefore effective in *monotherapy* for *refractory partial epilepsy*.

Summary of Findings

- **Topiramate**, 1000 mg/day superior to 100 mg/day, and is effective in *monotherapy* for *refractory partial epilepsy*.
- **Levetiracetam, tiagabine, or zonisamide**, there is insufficient evidence at present to determine the efficacy of in this population.

Summary of Findings

- **Gabapentin**, in one trial was not more effective than a “pseudoplacebo” dose of 600 mg in this population.
- The data from this study are not sufficient to generate a recommendation for the use of gabapentin in monotherapy for refractory partial epilepsy in these patients.

Conclusion

- The studies performed to demonstrate effectiveness of new AEDs in monotherapy in refractory partial seizure patients are difficult to interpret, because they are driven by FDA requirements to show superiority over placebo or “pseudoplacebo” rather than by clinical questions.

Conclusion

- Dosages used in the trials are often higher than those that might be used in practice, because the goal is to retain as many patients as possible and achieve a significant result.
- Most importantly, the goal of these studies is not to determine whether patients improve after they are converted to monotherapy. Rather, the goal is to determine whether they deteriorate less than the comparison group.

Recommendation

- Oxcarbazepine and topiramate can be used as *monotherapy* in patients with *refractory partial epilepsy* (**Level A**).
- Lamotrigine can be used as *monotherapy* in patients with *refractory partial epilepsy* (**Level B**, downgraded due to dropouts) .
- There is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine or zonisamide in monotherapy for refractory partial epilepsy (**Level U**)

Questions of Interests

1. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy*?
2. Are the new AEDs effective in *refractory partial epilepsy* as *monotherapy* ?
3. Are the new AEDs effective in *refractory idiopathic generalized epilepsy*?
4. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy* in children?
 - Are the new AEDs effective for *refractory idiopathic generalized epilepsy* in children?
 - Are the new AEDs effective for *Lennox-Gastaut syndrome* in children and/or adults?
 - What is the risk of teratogenicity with the new AEDs compared to the old AEDs?

Generalized Epilepsy

- Generalized epilepsy syndromes are categorized as idiopathic or symptomatic.
- Idiopathic epilepsy, also called 1⁰ generalized epilepsy, occurs on a presumed genetic basis, in the setting of normal brain structural architecture.
- Seizure types are limited to myoclonic seizures, generalized tonic-clonic convulsions, and absence (petit mal).

Generalized Epilepsy

- Idiopathic generalized epilepsy is easily treated, but response to treatment is very drug specific; some drugs, such as valproic acid are effective in over 80% of patients, whereas others, even those that are effective in partial seizures may be ineffective.
- In contrast, symptomatic epilepsy, also called 2⁰ generalized, is a devastating type of epilepsy in which developmental delay is typically present, and a structural abnormality is suspected or known.

Generalized Epilepsy

- One of the more common symptomatic epilepsy syndromes is the Lennox-Gastaut syndrome, characterized by mental retardation, multiple seizure types and characteristic EEG pattern of slow spike-wave.
- Since most trials of Lennox-Gastaut syndrome involve children and adults, results of trials for symptomatic generalized epilepsy are included in the paediatric section.

Generalized Epilepsy

- Evidence for effectiveness of the newer AEDs in the generalized epilepsy syndromes is not as readily available as evidence in the partial syndromes. Much of the available data are class IV.

Summary of Findings

- **Topiramate**, 6 mg/kg/day is effective for the treatment of *refractory generalized tonic-clonic convulsions* +/- other seizure types.
- **Gabapentin**, 1200 mg is *not effective* in *refractory generalized tonic-clonic seizures* in patients with primary or secondary generalized epilepsy.
- Definitive studies have not been performed with the other new AEDs in this epilepsy type.

Conclusion

- Trials for refractory generalized epilepsy have been criticized, due to the fact that not all patients were required to have an EEG demonstrating a generalized pattern. In most studies, patients could be included if they had a normal EEG. Therefore, it is possible that some of the enrolled patients actually had secondary generalized tonic-clonic convulsions.
- Since most patients with idiopathic generalized epilepsy are easily controlled with appropriate medication, refractory patients are rare. It is unclear how results in this population would translate to patients with similar syndromes, but non-refractory disease.

Recommendation

- Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children (**Level A**)
- There is insufficient evidence to recommend gabapentin, lamotrigine, oxcarbazepine, tiagabine, levetiracetam or zonisamide for the treatment of refractory generalized tonic-clonic seizures in adults and children (**Level U**)

Questions of Interests

1. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy*?
 2. Are the new AEDs effective in *refractory partial epilepsy* as *monotherapy*?
 3. Are the new AEDs effective in *refractory idiopathic generalized epilepsy*?
 4. Are the new AEDs effective in *refractory partial epilepsy* as *adjunctive therapy* in *children*?
- Are the new AEDs effective for *refractory idiopathic generalized epilepsy* in *children*?
 - Are the new AEDs effective for *Lennox-Gastaut syndrome* in *children* and/or *adults*?
 - What is the risk of teratogenicity with the new AEDs compared to the old AEDs?

Secondary Generalized Epilepsy or Lennox Gastaut Syndrome

- Patients with the Lennox-Gastaut syndrome have many seizures/day, some of which, such as atypical absence, are difficult to count.
- It is common to use reduction in drop attacks (tonic or atonic seizures) as the primary outcome variable. This is considered a clinically significant outcome, as drop attacks are one of the most dangerous seizure types, often leading to injuries.

Summary of Findings

- **Lamotrigine**, at doses adjusted for weight and valproic acid use, ranging from 50-400 mg/day, reduces seizures associated with Lennox-Gastaut syndrome.
- **Topiramate**, 6 mg/kg/day is effective in reducing drop attacks (tonic and atonic seizures) in patients with Lennox Gastaut syndrome.

Summary of Findings

- **Gabapentin, tiagabine, oxcarbazepine, levetiracetam or zonisamide**, to date, there is no class I or II evidence that they are effective.
- **Lamotrigine and gabapentin**, in case reports both worsened myoclonic seizures in some patients.

Conclusion

- Patients with Lennox-Gastaut syndrome are difficult to treat, and require drugs that are broad spectrum. They are also the population that is most prone to exacerbation by AEDs. For example, carbamazepine has been reported to cause seizure worsening in this group.
- Topiramate and lamotrigine appear to be effective in this population and should be considered for use.

Recommendation

- Topiramate and Lamotrigine may be used to treat drop attacks associated with the *Lennox Gastaut syndrome* in *adults and children (Level A)*.

Questions of Interests

1. Are the new AEDs effective in *refractory partial epilepsy as adjunctive therapy*?
 2. Are the new AEDs effective in *refractory partial epilepsy as monotherapy*?
 3. Are the new AEDs effective in *refractory idiopathic generalized epilepsy*?
 4. Are the new AEDs effective in *refractory partial epilepsy as adjunctive therapy in children*?
- Are the new AEDs effective for *refractory idiopathic generalized epilepsy in children*?
 - Are the new AEDs effective for *Lennox-Gastaut syndrome in children and/or adults*?
 - What is the risk of teratogenicity with the new AEDs compared to the old AEDs?

AEDs Teratogenicity (Food & Drug Administration's Position)

- The FDA has categorized AED medications into 2 classes, C and D.
 - Category C drugs have demonstrated teratogenicity in animals, but human risk is not known.
 - The newer AEDs are classified as category C.
- Phenytoin, carbamazepine and valproic acid are category D.
 - Category D drugs are those drugs for which related to teratogenicity in both animal and human pregnancies.
- In both categories, the recommendation remains the same: selection of AED in pregnancy should be decided upon risk –benefit ratio to seizure control.

AEDs Teratogenicity

CONVENTIONAL

(prior to 1990)

- phenobarbital (yes)
- primidone (yes)
- carbamazepine (yes)
- phenytoin (yes)
- valproate (yes)
- acetazolamide (yes)
- ethosuximide (not known)

NEW

- gabapentin (unknown)
- lamotrigine (favourable evidence)
- topiramate (unknown)
- tiagabine (unknown)
- oxcarbazepine (unknown)
- levetiracetam (unknown)
- zonisamide (unknown)
- methsuximide (unknown)
- felbamate (unknown)

Summary of AAN Evidence-Based Guidelines Level A or B Recommendation

AED	Partial adjunctive adult	Partial Monotherapy	Primary generalized	Symptomatic generalized	Pediatric partial
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	Yes*(only absence)	Yes	Yes
Levetiracetam	Yes	No	No	No	No

* Not FDA approved for this indication

Summary of AAN Evidence-Based Guidelines Level A or B Recommendation

AED	Partial adjunctive adult	Partial Monotherapy	Primary generalized	Symptomatic generalized	Pediatric partial
Oxcarbazepine	Yes	Yes	No	No	Yes
Tiagabine	Yes	No	No	No	No
Topiramate	Yes	Yes*	Yes	Yes	Yes
Zonisamide	Yes	No	No	No	No

* Not FDA approved for this indication

What Things You Do Not Want to Miss?

- D/D:
 - The different types of seizures:
 - Absence vs preoccupation
 - Complex partial vs confusion arousal
 - Frontal lobe seizure vs RESM sleep behaviour
 - Complex partial seizure vs psychosis
 - Atonic seizure vs syncope/fainting episode
- The newly available AEDs.

References

- Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy. *Neurology* 2004;62:1252.
- Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy. *Neurology* 2004;62:1261.

THE END

THANK YOU