

ANTICONVULSANT THERAPY:ADVANCES 2008

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NEW DRUGS FOR EPILEPSY 2008

- INTRODUCTION: new wine for old wineskin, or a CURE for an orphan?
- Historical Perspective: new AEDs
- Improved care for persons with epilepsy
- Diagnosis: EEG, MEG, neuroimaging
- Medical Treatment: AEDs, diet, vitamins
- Surgery: excision, section, stimulation
- Others: biofeedback, lifestyle changes.
- Novel interventions: seizure prediction?

OUTLINE OF NEW AEDS

- Lamotrigine (LMT): Lamictal®
- Levetiracetam (LVT): Keppra®
- Topiramate (TPM): Topamax®
- Oxcarbazepine (OxCBZ): Trileptal®
- Zonisamide (ZNS): Zonegran®

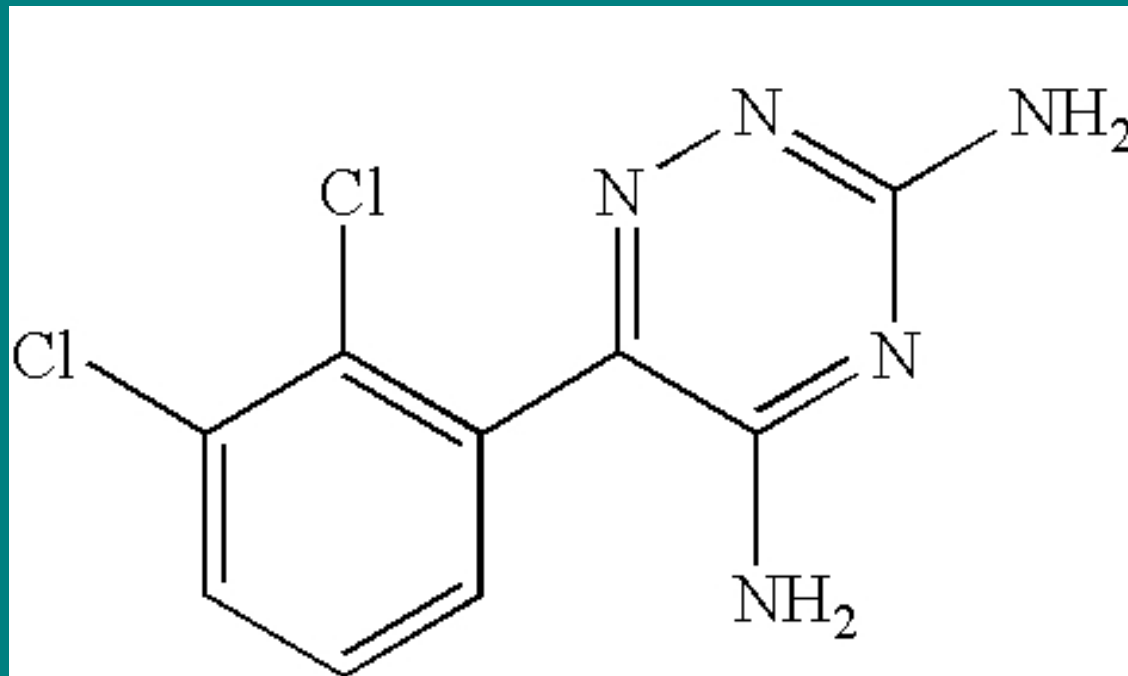
LAMOTRIGINE : example of a new antiepileptic drug (AED) : Lamictal ®

History of Lamotrigine (LMT)

- Hypothesis in the early 1960s : a relationship exists between the antifolate effect of the antiepileptic drugs (phenobarbital, phenytoin, primidone) and their therapeutic actions.
- Problems : antifolate compounds induce side effects of anaemia, thrombocytopenia and teratogenicity.
- Resolution of the problem : to modify the chemical structure in order to reduce antifolate properties and to increase antiepileptic effects. => synthesis of Lamotrigine : a weak folate antagonist.

Richens, A. 1992

Chemical structure :



[3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine]
BW430C

Clinical Applications

- Adjunctive Rx adults & children >2 y.o.
- Partial seizures, generalised seizures of Lennox-Gastaut S.: LD 0.1-0.6, MD 1-15mg/kg
- Monotherapy adult partial seizures: 12.5-50mg
- Adjunctive Rx primary GTC seizures >2y
- Increase myoclonic seizures of infancy
- Depression co-morbidity c epilepsy.
- Bipolar disorder maintenance treatment.

Adverse effects

- Generally mild, occur within the first 2 weeks, resolving without discontinuation of LMT.
- Most commonly adverse effects due to the use of adjunctive therapy with LAMICTAL (incidence of at least 10%): dizziness, headache, diplopia, somnolence, ataxia, nausea and asthenia.

CPS 2007

Severe Adverse effects

- Children on LMT (especially with VPA comed) are more likely to have severe ADRs, up to 20%: Stevens-Johnson Syndrome, generalised rash, liver and even multi-organ failure (Chattergoon et al. 1997).
- Warning : Abrupt discontinuation of any antiepileptic drug (AED) in a responsive patient with epilepsy may provoke rebound seizures.
- In general, withdrawal of an AED should be gradual, to minimize this risk. Unless safety concerns (i.e., rash) require a more rapid withdrawal .CPS 2007

Teratogenicity

- Theoretical risk of human fetal malformations if mother is treated with the drug during pregnancy because lamotrigine is a weak inhibitor of dihydrofolate reductase.
- However, toxicology data from animals and from pregnant women treated with lamotrigine have not shown any obvious drug-related teratogenicity in their fetuses.

R E Appleton 1996

Topiramate (TPM) Topamax ®

- Monotherapy for partial & primary GTC Szs in adults & children >10 years old.
- Adjunctive therapy in adults and children >2 years of age: LD 1-3mg/kg; MD 5-9mg/kg.
- Adjunctive Rx for Lennox-Gastaut > 2y.
- Children with atonic (drop) seizures
- Migraine prophylaxis : adults & children.
- ADRs: weight loss, paresthesiae, stones.

Levetiracetam (LVT)

- Keppra® is approved adjunctive Rx for partial Szs in adults & children > 4 years
- Primary generalised Szs in adults & children > 6 years of age;
- Myoclonic seizures in adults & children >12 years old; LD 10-20mg/kg; MD 40-60 mg/kg.
- Children with Lennox-Gastaut syndrome & absences.
- ADRs few and minor.

Oxcarbazepine (OxCBZ)Trileptal®

- Adjunctive treatment for partial & secondarily generalised seizures
- Adults and children > 6 years
- LD 15 mg/kg, MD 15-30mg/kg/day
- Inactive metabolite monohydrate
- ADRs: hyponatremia, SJS, TEN
- Chinese need HLA-B*1502 haplotype.

Other AEDs: Not approved in Canada (but in U.S.)

- Tiagabine, TGB (Gabatril®) USA
- Pregabalin (PGB) Lyrica®: partial Szs adjunctive Rx only
- Felbamate FBM (Felbatol®) USA LGS, partial sec. generalised. BM & liver failure 1:3000.
- Zonisamide (ZNS):
- Zonegran® USA
- Absences & myoclonic Szs
- Adults 100-600mg
- Children start 1-2mg/kg/d, 6-8mg/kg
- ADRs: SJS, TEN, dec. CBC, psychosis.
- Stirpentol: inhibits P450, in France only.

Principles of AED therapy

- The drug of choice depends on the seizure type(s), per ILAE classification (1989);
- Remember: “Start Low and Go Slow” to initiate therapy with a new AED (eg.LMT)
- Monitoring AED plasma levels is useful for compliance, adverse effects, interactions
- Stop treatment gradually, unless in an emergency: e.g.SJS, status epilepticus.

Monotherapy vs. Polytherapy

- Only about 60% of seizures respond to first AED of choice; another 20-30% to second, but try to withdraw first AED(polytherapy).
- Reassess early when necessary at 1-2 months (at least after 5 half-lives of AED)
- Adjunctive therapy may help 10% more control, but complete remission is rare.
- Accurate epilepsy or syndromic diagnosis needed for prognosis or etiology: genetic or symptomatic epilepses.

Drug Trials in Epilepsy

- For several decades, the ‘gold standard’ is the randomised controlled trial (RCT): double-blind placebo-controlled, parallel-group study.
- Result: new AEDs approved by FDA as add-on therapy in refractory CPSz, and sec. generalized seizures only.
- Dozens of RCTs of new AEDs with placebo controls, of questionable ethical acceptability, may form a valuable source of ‘historical controls’ for future RCTs of new AEDs, if withdrawal to monotherapy.

Withdrawal to Monotherapy

- A 'new kid on the block' in RCTs has been proposed by J. French et al. to the FDA for new AEDs (but not accepted by EU/Canada).
- The new AED is added to 1-2 standard AEDs in refractory patients with partial seizures.
- Once adequate control is achieved, the standard AEDs are withdrawn slowly.
- Efficacy of the new AED is tested as monotherapy with the patient as own control, compared with historical controls from placebo-studies of previous AEDs.

Future directions

- New AEDs to be tested by ‘withdrawal to monotherapy’ study design (PAH: ‘monotherapy by the back door’, eg. Canadian Clobazam Study CJNS 1995).
- Novel mechanisms of action: AMPA-R blockade (brivaracetam BRV, Phase III)
- Unknown mechanisms (serendipity): perampanel: possible neuroprotection.
- Gene therapy when epilepsy genes known: ADNFLE, JME, Lafora, channelopathies.
- Localised delivery of new AEDs to seizure focus in the brain (experimental, invasive).
- Dietary manipulations: ketogenic, MCT, PUFA, vitamins, minerals, etc.

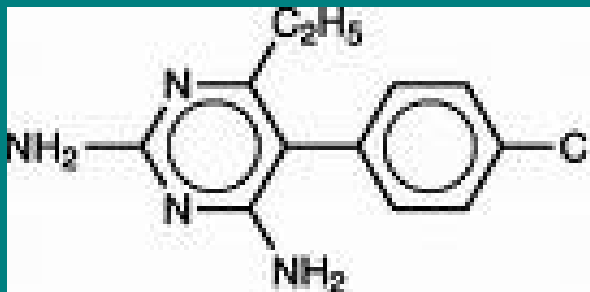
Thank you et Merci!

- “There are no diseases , only persons suffering from a particular disorder (such as epilepsy)”.
- Sir William Osler, Professor Emeritus of Medicine, McGill, Philadelphia, Johns Hopkins and Oxford Universities.
- (parentheses added for emphasis : PAH).

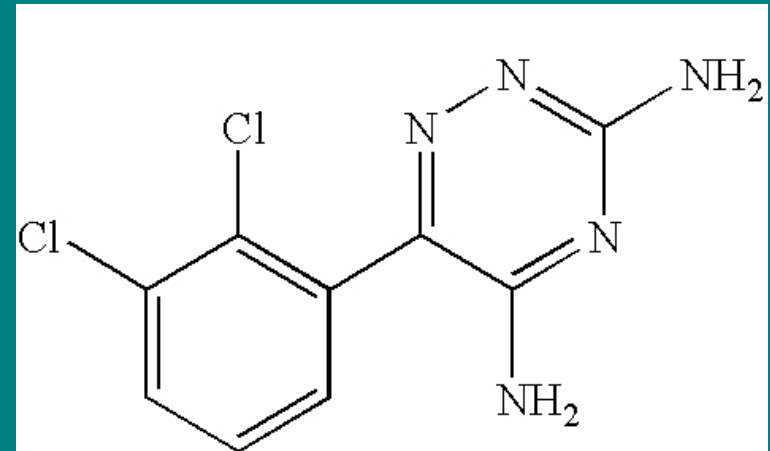
ACKNOWLEDGEMENT

- Nathalie Galy, Pharmacy student, Paul Sabatier Université de Toulouse (LMT);
- Prof. Mac Burnham and UTERP for stimulation all year, incl. several PhDs.
- Dr. Glenn Berall, Dept. Paediatrics, NYGH and Aurore Scouarnec, U.de Toulouse.
- Institute of Medical Science, SGS, U.of T
- Persons with epilepsy (PEC) and families who agree to participate in RCTs of AEDs.

Modification of pyrimethamine, an antifolate compound, to form lamotrigine



Pyrimethamine



Lamotrigine

Conversion of pyrimidine ring in triazine ring with three nitrogens
Modification of the substituting compounds

Pregabalin (PGB) Lyrica®

- Neuropathic pain: post-herpetic & trigeminal neuralgia, DM neuropathy.
- Efficacious for partial seizures (cf. GBP), approved in US, but not in Canada.
- Clean prodrug, minimal AEs, interactions
- LD 75 mg BID, MD 150-600mg/day
- Not on ODB, costly (not LU, ? Trillium).

Gabapentine (GBP) Neurontin®

- Adjunctive therapy for partial seizures +/- sec. generalised in adults and children >6 yrs: LD 10, LD 25-40mg/kg
- No hepatic metabolism, renal excretion
- Minimal drug interactions eg. macrolides
- Bipolar disorders, neuropathic pain.
- ADR: sleepiness, lack of efficacy (e.g. gen. Szs), cost (LU for Szs only).

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