



Merritt-Putnam Symposium 2006

Optimising epilepsy treatments in the pharmacogenomic age

Symposium highlights

EPILEPSY SOCIETY OF AUSTRALIA, Annual Scientific Meeting

Overview of current outcomes of AED treatment – efficacy and adverse effects



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Finding appropriate antiepileptic drugs (AEDs) for our patients goes beyond the efficacy of treatments in clinical trials. Both agent-related factors, such as side effects, interaction potential and teratogenicity, and patient-related factors, such as gender, age, genetics and comorbidities, must be considered. Nevertheless, only the seizure-specific efficacy or effectiveness of AEDs can be assessed in randomised controlled clinical trials (RCTs).

Older versus newer AEDs

About 60% of patients with newly diagnosed epilepsy treated for the first time will have their seizures controlled with monotherapy, with approximately half being seizure free with the first single agent drug tried and 13% with the second single agent, but only 4% with the third AED or a combination of two drugs (Figure 1).¹

In general, the efficacy of the newer agents and older agents are considered similar in seizure control.²⁻⁴ The available trial data comparing older and newer agents however have many shortcomings, including inadequate power, short study durations, fixed

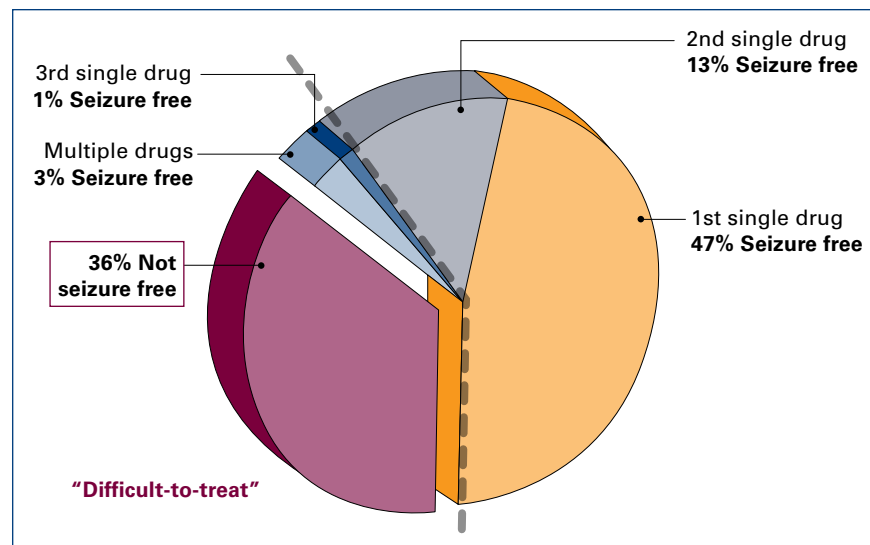


Figure 1. Approximately 60% of patients with newly diagnosed epilepsy become seizure free after trial of 1 or 2 AEDs. The remaining 40% are more difficult to treat.

titration schedules, mixed populations and questionable clinical endpoints. Recent systematic reviews of the clinical data by the American Academy of Neurology and the International League Against Epilepsy individually advised that there is little good-quality evidence to support the use of newer over older drugs as monotherapy, and that it is impossible to determine the relative effectiveness of the newer AEDs because of differences in the populations and the drug doses studied.^{2,3}

Cost-effectiveness considerations

Based on the limited data available, a recent UK economic analysis comparing newer and older agents found (with caveats about the uncertainty of the data) that for:⁴

Patients with partial seizures

- Older AEDs were more likely to be cost-effective as monotherapy for newly diagnosed patients than newer agents.
- Newer AEDs used as adjunctive therapy for refractory patients were more effective but more costly than continuing with existing treatment alone.
- Combination therapy involving newer AEDs may be cost-effective.

Patients with generalised seizures

- Lamotrigine and valproate showed similar health benefits when used as monotherapy.
- Valproate was less costly and was likely to be cost-effective.
- Topiramate might be cost-effective when used as an adjunctive therapy compared with continuing current treatment alone.

The ultimate choice of AED(s) for any individual patient with newly diagnosed or untreated epilepsy should include not only consideration of the available efficacy and effectiveness evidence but also factors such as the agent's safety and tolerability profile, pharmacokinetic properties, formulations and cost.

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Mechanisms of pharmacoresistance



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Although there is no universally accepted definition, most clinicians consider a patient's epilepsy pharmacoresistant if seizures continue to occur despite optimal treatment with three individual AEDs at maximally tolerated doses. Pharmacoresistance affects 30-40% of patients causing significant health and socioeconomic burden. The resistance is broad spectrum, with resistance to most, if not all AEDs, including the newer agents. The mechanisms are poorly understood but some clinical features associated with resistance include symptomatic or cryptogenic epilepsy, early onset of seizures (before 1 year of age), high seizure frequency prior to onset of treatment, failure of control with the first AED, EEG and structural brain lesions and disorders of cortical development. Factors not predicative include early treatment and the type of AED used first.

There are numerous potential causes for refractory epilepsy and it is likely to be a multifactorial process. Possible underlying mechanisms may involve absorption, metabolism and brain uptake of AEDs, modification of cellular drug targets, modulating factors in the brain, and inherent disease factors. Genetic factors, such as polymorphisms, may be important in explaining why two patients with the same type of epilepsy or seizures differ in their response to AEDs.

Multidrug transporter polymorphism

The broad nature of pharmacoresistance suggests that nonspecific mechanisms, such as decreased drug uptake into the brain by multidrug transporters may be involved. These transporters are adenosine triphosphate-binding cassette (ABC) proteins in the endothelial cells of the blood-brain barrier. They direct active efflux mechanisms and appear to limit accumulation of many lipophilic drugs in the brain. There is some animal data suggesting that transporters are involved in the passage of AEDs into the brain, but the evidence is conflicting and many of the >50 transporters have not been studied.

Some possible sites of pharmacoresistance to AEDs

- Drug absorption
- Drug metabolism: eg, cytochrome polymorphism
- Brain uptake: eg, multidrug transporter polymorphism
- Cellular drug targets: eg, receptor polymorphism or acquired receptor changes
- Modulating factors in the brain: eg, cytokines and endorphin precursors
- Inherent disease factors: eg, cortical dysplasias

Increased expression of transporters in patients with pharmacoresistant epilepsy does occur and there is evidence that increased expression is associated with poor seizure control. Moreover, there is some evidence that inhibiting the transporters might decrease resistance, at least in animal models. However, there do not appear to be clear consistent associations between genotypes and drug-resistant epilepsy.

Alteration in cellular drug targets

Another possible explanation for pharmacoresistance are changes in drug-targets. This involves intrinsic or acquired loss of brain-target sensitivity. This hypothesis is largely based on studies with carbamazepine and the voltage-gated sodium channels in hippocampal neurones. But the loss of sodium channel sensitivity seen with carbamazepine in refractory epilepsy does not occur with other AEDs that affect sodium channels, such as valproate and lamotrigine, so it may only be part of the story. More recently there are data to suggest that genetic polymorphism may be involved in levetiracetam resistance, with genetic

variation in synaptic vesicle protein 2A, (the primary binding site for levetiracetam) affecting response.

Inherent disease factors

Increased epileptogenicity due to changes in neuronal networks or neuronal modification is another proposed mechanism. Loss of inhibitory neurones, loss of excitatory neurones that stimulate inhibitory neurones, aberrant neuronal sprouting with autoexcitation or generation of new neurones are just some of the possible neuronal network changes that might cause an inappropriate hypersynchronous, burst firing response of a population of neurons to a stimulus. All these are known to occur in temporal lobe epilepsy, which is often treatment resistant. Also changes in the neurones themselves, such as changes in GABA function, may also lead to treatment resistance.

In conclusion, there are many possible causes of refractory epilepsy and it is likely to be a multifactorial process. Disease-related factors are certainly important, but other mechanisms are likely to contribute to treatment resistance including changes in drug targets and drug uptake into the brain.

Acknowledgement

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Further reading

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AEDs and fracture risk



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Factors contributing to fracture risk

The adverse effects of AEDs on bone health were first reported in the 1960s and since then a mounting body of evidence has linked a variety of biochemical, metabolic and radiologic abnormalities in bones to the use of AEDs.¹ Early studies suggested that this may be due to vitamin D deficiency: how-

ever, it is now considered to be far more complicated with many factors contributing. Hormonal abnormalities, renal, bone and gastrointestinal defects, and abnormal vitamin D metabolism all may be involved in decreasing bone mass and strength (osteoporosis), and bone mineralisation (osteomalacia) in people taking long-term AEDs (Figure 1, over).¹

AED-related bone disease

Regardless of the aetiology, the morbidity and significant mortality associated with osteoporosis and fracture (especially in older patients) is likely to increase as more patients are prescribed AEDs not only for epilepsy but also for chronic pain and

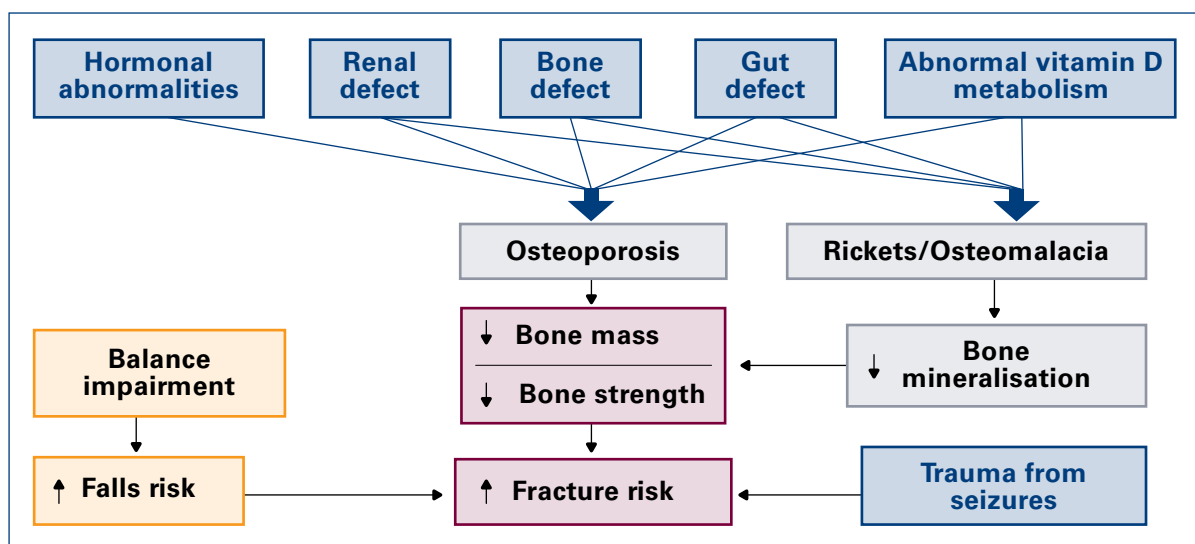


Figure 1. Multifactorial aetiology of AED-related fractures.⁸

psychiatric conditions. Nevertheless, there appears to be a lack of awareness among physicians about these effects and relatively few neurologists evaluate their AED-treated patients let alone consider preventative treatment for osteoporosis. This may be partly explained by the quality of the older data regarding bone loss and the paucity of information on newer anti-convulsants. However, there are a number of recent studies that consistently demonstrate at least a doubling in fracture risk in patients taking long-term AEDs.²⁻⁴ In fact, a review of data from the UK General Practice Research Database found that the risk associated with AEDs was higher than with glucocorticoids.³ Further, in the large longitudinal US Study of Osteoporotic Fractures, there was a 1.6-fold increase in adjusted annual bone loss in continuous user of AEDs compared to non-users.⁵ Twin and sibling studies also show a significant deficit in bone mineral density (BMD) with AED use, with significant, within pair differences in BMD in older women receiving long-term inducer AED therapy.⁶ Very limited data suggest that older (inducer) and newer (non-inducer) AEDs may have similar fracture risk.⁷

In conclusion, AEDs are a major iatrogenic cause of fractures at least in part because of effects on bone

mass and strength. Considerable research is needed to fully understand the mechanisms involved, the clinical presentations and outcomes of bone loss, and whether older and newer AEDs have different effects. Currently, there are no evidence-based strategies for the prevention and treatment of AED-related bone disorders and treatment remains largely empirical using standard osteoporosis therapies.

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Discussion

Q. What mechanism might be involved given that both older and new agents seem to be implicated?

A. The mechanistic data are quite old and mainly involve only inducer AEDs, but given the disparate pharmacology of these drugs, the concept of a unifying class effect that influences bone is attractive, whether it be at the bone or CNS level.

Q. What should we as clinicians be doing to monitor our epilepsy patients?

A. On general principles, addressing risk factors for osteoporosis and measuring vitamin D levels are probable first steps. Monitoring BMD is the most useful surrogate marker for assessing fracture risk and, even though Medicare would not initially cover this, patients prescribed long-term AEDs should be screened at baseline and probably at 2-yearly intervals.

Sex hormones, sexuality and fertility: effects of epilepsy and its treatments



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Women with epilepsy have a number of management problems related to reproductive hormones. Many women with epilepsy experience changes in seizure frequency and severity at puberty, with pregnancy and at menopause. Moreover both AEDs and epilepsy itself can influence a woman's reproductive choices.¹ Oestrogen and progesterone both influence neuronal excitability and therefore can affect the seizure threshold. Oestrogen reduces inhibition at γ -aminobutyric acid (GABA-A) receptors, enhances excitation at the glutamate receptor, and increases the number of excitatory neuronal synapses. Progesterone enhances GABA mediated inhibition, increases GABA synthesis, and increases the number of GABA-A receptors.¹

Contraception challenges

Antiepileptic therapy limits a woman's contraceptive choice because most AEDs induce the hepatic microsomal enzymes increasing the metabolism of the combined oral contraceptive pill and also increasing the protein binding of the hormones.^{1,2} This reduces contraceptive efficacy (Table 1).³ Women with epilepsy taking inducer AEDs have at least a 6% failure rate per year for oral contraceptives.¹ The more effective contraceptive options for woman receiving an inducer AED, are progesterone depot injections (eg, Depo Provera), intrauterine devices (copper or hormonal) and barrier methods. High-dose combined-oral contraceptive pills (COCP), which can provide suitable contraception for women with epilepsy (ie, contain at least 50 μ g oestradiol^{1,2}), are not longer available in Australia.

Management of catamenial epilepsy

For approximately 70% of women there is a relationship between their epilepsy and menstrual cycles, and up to 40% of women with epilepsy have catamenial seizure patterns.^{4,5} Three patterns have been described:⁵

- Seizures most likely to occur in the perimenstrual period
- Seizures most likely at ovulation
- Seizures more random and severe during anovulatory cycles

Agents that may compromise oral contraceptive efficacy

Carbamazepine

Ethosuximide

Lamotrigine

Oxcarbazepine

Phenobarbitone

Phenytoin

Tiagabine

Topiramate

Valproate

Zonisamide

Agents that do not affect oral contraceptive efficacy

Clonazepam

Gabapentin

Levetiracetam

Pregabalin

Vigabatrin

This is not a comprehensive list. Please review the product information of the agents outlined in the above table for further detail.

Table 1. Antiepileptic drug effects on oral contraceptives³

Although there are no approved hormonal treatments, suppressive and cyclic hormonal therapies are used. Suppressive options include progesterone depot/implants or continuous use of a COCP, while the cyclic option involves using progesterone in the luteal phase. Two open label trials suggest that a cyclical approach can be effective, although the rationale remains unclear.

Counselling considerations

Some women with epilepsy will opt not to have children because of concerns about AED-related birth defects.^{1,2} Overall the risk of birth defects is two- to three-fold higher among women taking AEDs compared to the general population, with the risk increasing as the number of AEDs taken increases. Major congenital abnormalities associated with older agents include cleft lip and palate, and ventricular-septal defect, while minor abnormalities mainly involve the face and digits. Neural tube defects (NTDs) are associated with exposure to valproate and

carbamazepine, occurring at rates of 1-2% and 0.5-1% respectively. There is also evidence of behavioural and cognitive defects in children exposed to valproate in-utero.² In general, because valproate appears to be associated with a higher incidence of congenital abnormalities compared to other AEDs, consideration should be given to using agents other than valproate in women of child-bearing age who wish to fall pregnant.² Also where possible, a single AED should be used to manage epilepsy during pregnancy.^{1,2}

Given that the effects of seizures on the foetus may be greater than the potential for AED-related congenital abnormalities, it is important that pregnant women do not stop their antiepileptic medication. Seizure frequency is increased during pregnancy in about one third of women with epilepsy, although this may be partly due to poor medication compliance and changes in AED pharmacokinetics.¹

Supplements are another issue to consider when counselling women with epilepsy during or before pregnancy:^{1,2}

- Extra folic acid supplements are advised (5 mg instead of the usual 0.4 mg) because AEDs may interfere with folic acid metabolism. NTDs are associated with low folate levels.
- Vitamin K supplements in the last month of pregnancy are recommended to prevent neonatal haemorrhage. Inducer AEDs lower the plasma levels of the Vitamin K dependant clotting factors.

Reproductive consequences of obesity and polycystic ovarian syndrome (PCOS)

Between 20-40% of women with epilepsy have polycystic ovaries,¹ and 13-25% have PCOS,⁶⁻¹⁰ which causes irregular periods and hyperandrogenism. In

comparison, 5-10% of women in the general population have PCOS, which is usually linked to obesity. However in studies examining epilepsy and PCOS there has been no consistency in the method of diagnosis and this is particularly pertinent as there are now two different criteria to make the diagnosis of PCOS. Drugs that cause weight gain, such as valproate, have the potential to cause PCO. There is no conclusive evidence that women taking valproate are at greater risk of PCO, if they do not gain weight.

In conclusion, women with epilepsy will often see a gynaecologist or a reproductive endocrinologist as well as an epileptologist. Treating these women successfully requires a close working relationship between the specialities.

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Discussion

Q. What should we be telling women regarding AEDs and breastfeeding?

A. AEDs are transferred into breast milk to varying degrees, so it may be best to limit breastfeeding to the first 6 weeks of life. The benefits of breastfeeding for the neonate are considered to outweigh the potential risks of AED exposure.

Q. As neonatal haemorrhage may not really be an issue, is there a downside to Vitamin K supplements?

A. No there are no problems associated with Vitamin K supplements.

AED treatment in children: growth, obesity and bone metabolism



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Treatment aims in children with epilepsy go beyond controlling seizures and quality of life issues. The standard paediatric goal of maximising physiologic development, specifically linear growth, body mass and bone mineral accrual, also need to be considered, including how these are affected by AEDs.

Impact of AEDs on linear growth

Unfortunately, information about impaired growth in children with seizure disorders is conflicting. However some good data are available from a recently published Finnish study that compared growth and body mass index in girls with epilepsy at 12.7 years and 17-19 years of age. The girls were initially taking valproate, carbamazepine or oxcarbazepine. The study found that neither epilepsy nor antiepileptic therapy adversely affected linear growth or final height, but AEDs may have unfavourable effects on body weight, particularly in girls taking valproate.¹

Impact of AEDs on body mass

Adult data indicates that AEDs have varying effects on bodyweight, with drugs such as valproate, carbamazepine and gabapentin being associated with weight gain, while others are weight neutral or even weight sparing due to mild appetite suppression (Table 1).^{2,3} Weight gain appears to be most associated with puberty, and of particular concern, is that weight gain with valproate appears not to plateau.

AEDs and impaired bone mineral accrual in childhood

Although the exact mechanisms for the adverse bone effects of AEDs are still to be explained, AEDs are

Weight neutral	Weight gain	Weight loss
Lamotrogine	Carbamazepine*	Felbamate
Levetiracetam	Gabapentin*	Topiramate
Phenytoin	Valproate*	Zonisamide
	Vigabatrin	
	Pregabalin	

* Also in children and adolescents

Table 1. AEDs with demonstrated effects on body weight in adults^{2,3}

known to influence and modify bone mineralisation in many ways through altered Vitamins D and calcium metabolism and hyperparathyroidism.⁴

Measuring bone mineral density (BMD) in children has some limitations. Firstly for practical reasons, measurement is limited to children over 6 years of age because they are required to remain still. Secondly with standard DEXA (Dual Energy X-ray Absorptiometry) methods there needs to be an allowance for the child's height. DEXA measures areal density (gm/cm²) rather than true volumetric density (gm/cm³) and areal density is affected by size.

While this is not an issue in adults, shorter children have lower than expected areal bone densities than taller children of the same age. Thirdly the 'z score' (number of standard deviations different from the mean for their age and sex) should be used to measure BMD rather than the 't score' (number of standard deviations different from normal peak values) since children have not reached their peak bone mass. Also remember to consider a child's physiologic maturity/pubertal status when interpreting BMD studies.

In managing seizure disorders in child, the priority remains control of seizures, because these can be life-threatening events. AED are frequently used in brain-injured children with and without metabolic disturbances and at times it can be difficult to tease out what is causing a child's physiologic problems. AEDs probably do not affect linear growth and this needs to be addressed directly. Conversely, AEDs can affect body mass, so in managing a child's weight it may be helpful to consider weight neutral or sparing AEDs. AEDs can also cause bone loss and increased risk of fracture. Older and new agents appear to share this side effect, and management includes ensuring adequate calcium and Vitamin D intakes, maximising weight bearing exercise, reducing falls and surveillance with baseline and repeat BMD scans.

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AED treatment in children: influence of comorbidities and cognitive side effects on choice of drug



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Parents often attribute their child's learning and behaviour problems to antiepileptic drugs (AEDs) and this can significantly influence whether the child continues treatment for epilepsy. However other factors, such as the child's age and state of brain maturation; type, frequency and severity of seizures; comorbid disabilities; the underlying cause of epilepsy; as well as psychosocial and genetic factors are important contributors to the child's cognitive state (**Figure 1**). Unfortunately, the cognitive effects of AEDs in children have been inadequately studied. There are relatively few prospective studies; most have small numbers or methodical flaws.

Studies investigating the effects of newer AEDs on cognition and behaviour are very limited and it is not possible to compare the effects of new and old antiepileptics.^{4,5} Of the newer agents, topiramate and lamotrigine have the most data; topiramate has been shown to have negative effects on cognitive function, while lamotrigine may have positive effects in some children.^{4,5}

In general, child's baseline cognitive status is probably more important than the AED she/he is taking in determining the presence of cognitive and behavioural deficits.

Neuropsychological effects of in-utero AED exposure

There is some evidence that in-utero exposure to AEDs, particularly to valproate, may increase the incidence of cognitive problems. Several studies have suggested that children exposed to valproate mono-

therapy had significantly lower IQ scores when compared with children exposed to carbamazepine or phenytoin monotherapy. However the number of tonic-clonic seizures during pregnancy and low maternal IQ also adversely affected IQ.⁶

In summary, higher order cognitive deficits including attentional, memory, concentration, processing and behavioural problems have been described with older AEDs but the effect is usually mild except for phenobarbitone. Despite

the disappointing lack of evidence, it is likely that genetic and environmental factors play a more important role in predisposing certain children with epilepsy to cognitive and learning problems. Children with epilepsy are more likely to have cognitive and behavioural problems than age-matched controls but they do not usually deteriorate after starting AEDs or improve on stopping AEDs. This suggests AEDs have a limited adverse effect on higher order cognitive function.³

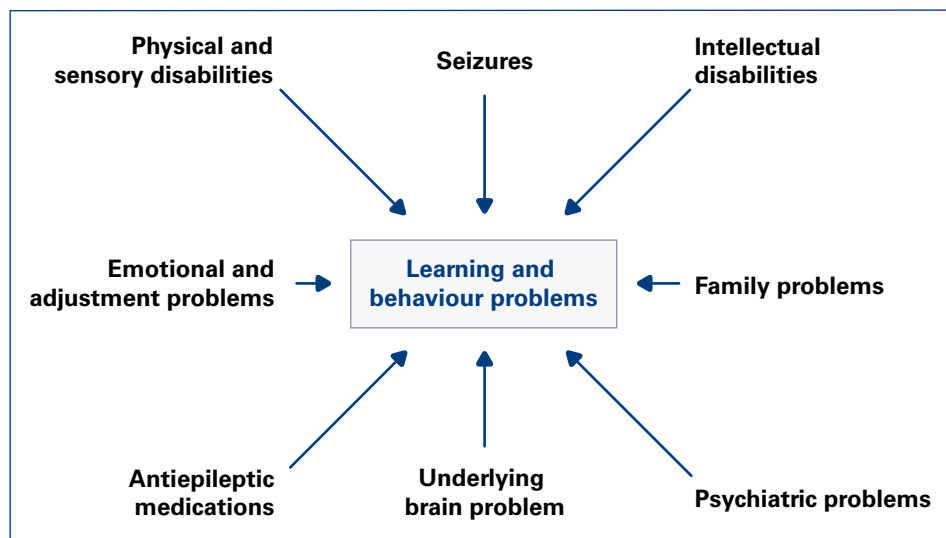


Figure 1. Factors affecting cognition and behaviour in children with epilepsy.

Effects of older and newer agents on cognition

With the exception of phenobarbitone, studies have not shown a significant adverse impact on IQ with older AEDs. In studies, children taking phenobarbitone had declines in IQ, and although this improved following discontinuation of the drug,¹ there continued to be long-term problems with learning development when these children were tested 3-5 years later.² This suggests that the cognitive problems may not be recoverable.^{3,4} The cognitive side effects of carbamazepine, phenytoin and valproate are comparable and associated with modest decreases in attention, memory and/or processing speed.^{3,4}

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Pharmacogenetics – is it the future?



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Epilepsy ideal for pharmacogenetic studies

Differences in drug metabolism and action in patients give rise to wide variation in individual responses to drug treatment. Pharmacogenetics is the study of genetic causes of these variations in drug response and focuses primarily on single nucleotide polymorphisms (SNPs), which are single base variations in the gene sequence. These have the potential to influence the structure and/or function of the proteins (phenotype) encoded by the gene.

Some of the factors that make epilepsy an ideal arena for the application of pharmacogenetics include:¹

- The disease prevalence – epilepsy is relatively common
- Quantifiable response to AED
- Well-documented pharmacodynamics and kinetics of AEDs
- Dichotomous outcomes – pharmacosensitive *vs* pharmacoresistant, adverse effects *vs* no adverse effects.

Pharmacogenetics limitations

However, recent studies of associations between specific AED responses (eg, seizure control and adverse effects) and relevant genetic variants have been disappointing. For example, an initial finding of an association between polymorphism in the drug-transporter gene ABCB1 and pharmacoresistance in epilepsy patients could not be duplicated.^{2,3}

Although the technology is adequate, there are currently problems with a lack of standardisation in epilepsy definitions (eg, seizure types, pharmacoresistance, seizure control), the methodologies and statistical analyses (eg, inadequate sample size, lack of appropriate stratification and information on confounders) used in studying AED response.

Moreover the multifactorial complexity of epilepsy makes it difficult to identify what genes are operating; there are many genes involved in AED metabolism and pharmacodynamics and it is likely that a number of genes and effects are involved in any given process.

Future work needs to account for these factors as well as other influences such as ethnic variations in genotypes, gene interactions, polygenic effects, and the up or down regulation of the genes involved by the drugs and/or disease. These requirements will necessitate large cohorts with multi-centre collaboration. A pharmacogenetic approach to treating epilepsy has the potential to help reduce the burden of disease, improve the tolerability of AEDs, optimised use of medical service, save costs for both patients and communities, and improved patient quality of life.

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Which drug – now and tomorrow?



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Good clinical practice combines clinician training and experience, patients' preferences and values and judicious use of evidence-based treatments. Unfortunately there is minimal scientific evidence for the efficacy and safety of AEDs in specific epilepsy syndromes and so we rely on extrapolating data from studies of different seizure types. This lack of data was highlighted in the International League Against Epilepsy (ILAE) treatment guidelines, which attempted to provide an evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.

ILAE treatment guidelines

In preparing the guidelines, a 10-member subcommission of the Commission on Therapeutic Strategies of ILAE evaluated articles dealing with different seizure types (for different age groups) and two epilepsy syndromes.

Table 1. Summary of the International League Against Epilepsy (ILAE) treatment recommendations for initial monotherapy for epileptic seizures and syndrome and the strength of these recommendations¹

Seizure type	Recommended antiepileptic drugs					
	Level A	Level B	Level C	Level D	Level E	Level F
Adults with partial onset seizures	CBZ, PHT	VPA	GBP, LTG, OXC, PB, TPM, VGB	CZP, PRM	Others	None
Children with partial onset seizures	OXC	None	CBZ, PB, PHT, TPM, VPA	LTG, VGB	Others	None
Elderly with partial onset seizures	GBP, LTG	None	CBZ	TPM, VPA	Others	None
Adults with generalised onset tonic-clonic seizures	None	None	CBZ, LTG, OXC, PB, PHT, TPM, VPA	GBP, VGB	Others	None
Children with generalised onset tonic-clonic seizures	None	None	CBZ, PB, PHT, TPM, VPA	OXC	Others	None
Children with absence seizures	None	None	ESM, LTG, VPA	None	Others	CBZ, GBP, OXC, PB, PHT, TGB, VGB
Children with BECTS	None	None	CBZ, VPA	GBP, STM	Others	None
Juvenile myoclonic epilepsy	None	None	None	CZP, LTG, LEV, TPM, VPA, ZNS	Others	CBZ, GBP, OXC, PHT, TGB, VGB

Level A, established; B, probably; C, possibly; D, potentially effective; E, no data; F, ineffective or significant risk of seizure aggravation

CBZ, carbamazepine; CZM, clonazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbitone; PHT, phenytoin; PRM, primidone; STM, sulthiame; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate; ZNS, Zonisamide

The quality of evidence was assessed based on predefined criteria:¹

- **Class I:** double-blind randomised controlled trial (RCT) design: ≥ 48 -week treatment duration without forced exit criteria: information on ≥ 24 -week seizure freedom data (efficacy) or ≥ 48 -week retention data (effectiveness): demonstration of superiority or 80% power to detect a $\leq 20\%$ relative difference in efficacy/effectiveness versus an adequate comparator; and appropriate statistical analysis.
- **Class II:** studies met all class I criteria except for having either treatment duration of 24 to 47 weeks or, for noninferiority analysis, a power to only exclude a 21-30% relative difference.
- **Class III:** studies included other randomised double-blind and open-label trials.
- **Class IV:** other forms of evidence, eg, expert opinion, case reports.

The quality of clinical trial evidence was used to determine the strength of the ILAE guidelines' recommendation:

- A: established efficacy
- B: probably effective
- C: possibly effective
- D: potentially effective
- E: no data of efficacy; and
- F: ineffective or significant risk of seizure aggravation.¹

Only four of 50 RCTs evaluated had class I evidence, two had class II evidence and the remainder had only class III evidence. Only three seizure types had AEDs with level A or level B efficacy and effectiveness evidence as initial monotherapy: adults with partial-onset seizures, children with partial-onset seizures and elderly adults with partial-onset seizures. There was no level A or B evidence for AEDs in the remaining seizure types and syndromes (Table 1, page 10).¹

In general, the data for initial therapy of patients with generalised seizures/epilepsies were poor. The studies had problems with inclusion criteria with seizure types rather than syndromes being studied. There was little or no dosing flexibility, short follow-ups, questionable endpoints and notable design biases. Nevertheless, perhaps the most concerning issue was that the majority of syndromes and seizure types were never studied. Hopefully in the future, we will be able to accurately identify epilepsy syndromes in terms of their aetiology using imaging and genetic data, and treatments will be evaluated in these specific syndromes. This is already being done for some rare genetically-determined epilepsy syndromes under the auspices of the European Union's orphan medicinal products initiative.

Reference

1. Glauser T, *et al.* ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006; 47: 1094-120.

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Please consult approved Australian product information before prescribing.
The Lyrica PI accompanies this newsletter.

PBS Information: Lyrica is not listed on the PBS



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Neuropathic pain: LYRICA indicated¹

 **Rapid[†] and sustained[§]
pain reduction¹⁻⁵**

 **Rapid[†] improvement in disturbed
sleep, sustained[§] over time¹⁻⁵**

 **No clinically significant
pharmacokinetic drug interactions^{1#}**

PBS Information: This product is not listed on the PBS.

[†]Significant improvement compared to placebo by week 1. [§]Sustained effect for up to 13 weeks in clinical trials. ¹ #No pharmacokinetic drug interactions observed between LYRICA and commonly used drugs, including oral contraceptives (norethisterone/ethinyloestradiol), oxycodone[‡], ethanol*, lorazepam*, diuretics, oral hypoglycaemic drugs, insulin, antiepileptic drugs. [‡]Despite no pharmacokinetic interactions, LYRICA appears to be additive in the impairment of cognitive and gross motor function when co-administered with oxycodone. *LYRICA may potentiate the effects of lorazepam and ethanol.¹ Before prescribing, please review Approved Product Information. Product Information is available from Pfizer Australia. **LYRICA[®] Indications** Neuropathic pain in adults. As adjunctive therapy in adults with partial seizures with or without secondary generalisation. **Contraindications** Hypersensitivity to pregabalin or excipients. **Precautions** Pregnancy; lactation; may cause dizziness and somnolence and therefore may effect ability to drive and use machines and may increase the accidental falls in elderly; congestive heart failure; galactose intolerance; withdrawal symptoms. **Adverse effects** Dizziness, somnolence, blurred vision, weight gain, peripheral oedema, creatine kinase elevation, fatigue, dry mouth, ataxia, balanced impaired, diplopia. **Dosage** The dose range is 150 to 600 mg daily given as 2 divided doses. Neuropathic pain: Start at a dose of 150 mg per day, given as two divided doses. After 3 to 7 days, the dosage may be increased to 300 mg per day given as two divided doses. If needed, after an additional 7 day interval, the dosage may be increased to a maximum dose of 600 mg per day. Epilepsy: Start at a dose of 150 mg per day, given as two divided doses. After 1 week, the dosage may be increased to 300 mg per day given as two divided doses. If needed, after an additional 7 day interval, the dosage may be increased to a maximum dose of 600 mg per day. Dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance. For patients receiving haemodialysis, in addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis. Treatment discontinuation should be done gradually over a minimum of one week.

Use in children and adolescents (<18 years of age) have not been established. Further information is available from Pfizer Australia Pty Limited, ABN 50 008 422



348, 38-42 Wharf Road, West Ryde, NSW 2114. *LYRICA[®] Registered trademark of Pfizer. Pfizer Medical Affairs 1800 675 229. 1. LYRICA Approved Product Information. 2. Dworkin FH et al. *Neurology* 2003; 60: 1274-1283. 3. Rosenstock J et al. *Pain* 2004; 110: 628-638. 4. Lesser H et al. *Neurology* 2004; 63: 2104-2110. 5. Sabatowski R et al. *Pain* 2004; 109: 26-35. 05/07 PFXYL7163-C

LYRICA[®]
PREGABALIN

Fast onset. Sustained relief.¹